# PSYCHOPHYSIOLOGICAL INDICATORS OF DYSFUNCTIONAL INHIBITORY CONTROL IN REPETITIVE BEHAVIORS

by

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## ABSTRACT

The relationships among repetitive behaviors remain uncertain. While phenotypic distinctions have long maintained their disparate categorizations in the DSM, repetitive behaviors frequently overlap in phenomenology, neurobiology, and comorbidity. It has been suggested that dysfunctional inhibitory control may account for commonalities across these presentations. However, evidence from obsessive-compulsive disorder (OCD) and trichotillomania (TTM) suggests that, in fact, there may be heterogeneity of inhibitory control dysfunction across repetitive behaviors. In concert with NIMH's Research Domain Criteria (RDoC) initiative to better capture associated mechanisms of dysfunction, the present study aimed to determine if the patterns of inhibitory control dysfunction found in OCD and TTM extend to other repetitive behaviors. The study integrated event-related potential (ERP) methodology with observable symptoms to examine inhibitory control in neurodevelopmental disorders characterized by repetitive behaviors (RBs; i.e., tic disorders and autism spectrum disorders). Seventy-six children (43 with RBs; 33 typically developing controls) were asked to complete two tasks targeting inhibitory control processes in two contexts: the Ericksen Flanker Task (EFT), which measured interference control, and the Stop-Signal Task, which tapped motor inhibition. In these contexts, ERPs captured two stages of inhibitory control: conflict monitoring (error-related negativity [ERN], "no-go" N2) and conflict resolution (error positivity [Pe], "no-go" P3). Despite observing expected within-person effects across

behavioral measures and other ERP components, results largely indicated that individuals with RBs demonstrated intact inhibitory control, as measured by these tasks. There was a single between-group effect in conflict resolution during interference control, such that individuals with RBs had a smaller magnitude differential between Pe and Pc, suggesting less subjective awareness of errors. However, this effect should be interpreted with caution, as it did not hold across a second analysis procedure. Collectively, results indicate that inhibitory control deficits are likely not unidimensional, but instead are specific to the stage of control and the context in which control is taxed. Moreover, the specific deficits appear to vary across repetitive behaviors. Diagnostic and treatment implications are discussed.

# Chapter 1

# INTRODUCTION

## Classification of Repetitive Behaviors

Repetitive behaviors are considered adaptive during early development (Piaget, 1952). Typically-developing young children frequently become preoccupied with ordering objects, attach themselves to one object, prefer routines and repetitive games, repeatedly groom, and demonstrate awareness of details (Boyer & Liénard, 2006). It is theorized that such repetitive behaviors function to decrease anxiety and allow children to accommodate and organize new information as they gain mastery over their environments (Evans, et al., 1997; Gesell, Ames, & Ilg, 1974). However, while adaptive during early development, these repetitive behaviors bare remarkable similarities to the repetitions that characterize a number of psychopathological presentations in later years.

In psychopathology, the domain of repetitive behaviors is characterized by repetition, rigidity, invariance, and inappropriateness (Turner, 1999). Presentations are largely heterogeneous and include recurring thoughts and associated responses (obsessive-compulsive disorder), excessive risking of possessions (pathological gambling disorder), as well as repetitive hair-pulling (trichotillomania), skin-picking (excoriation disorder), vocalizations and motor movements (tic disorders, autism spectrum disorders), and use of objects (autism spectrum disorder). As our current diagnostic system is based

on observable symptoms, phenotypic distinctions have maintained these repetitive behaviors as different diagnoses in the DSM-V. However, heightened levels of comorbidities among these disorders (Canitano & Vivanti, 2007; Robertson & Stern, 1997), as well as heterogeneous presentations within diagnostic categories, give pause to these classifications.

A recognized limitation of the current diagnostic system is that it fails to characterize associated mechanisms of dysfunction. As a result, the National Institute of Mental Health (NIMH) has devised a new classification framework called Research Domain Criteria (RDoC; Insel et al., 2010) to better capture mechanisms associated with psychopathology. The framework is organized into five domains of functioning, which are to be examined across multiple units of analysis ranging from genes to overt behaviors. By integrating neuroscience findings with observable behaviors, NIMH's goal is to determine neurobiological mechanisms associated with the spectrum of typical to atypical phenotypes, hence grounding both psychological diagnosis and treatment in empirical data. In line with the RDoC initiative, the goal of the proposed study was to identify mechanisms of dysfunction that are common to, and/or distinct in, various presentations of repetitive behaviors. Such a study would lead to an improved understanding of the specificities of inhibitory control dysfunction, provide data towards improving the current diagnostic system, and lead to the refinement of empirically-supported treatments.

## Inhibitory Control

On an average day, in the midst of progress towards daily goals, we each experience distractions and intrusions that culminate in urges and conspire to impede our progress towards our goals. We are expected to maintain mindful attention to a class lecture, despite urges for attention to waver to anxiety about an upcoming assignment or to nearby peers whispering about the newest episode of a beloved television show. When window-shopping and confronted with highly-desired item, we are challenged to maintain our budget and not purchase it. When faced with seemingly unwarranted criticism from a colleague that generates an urge to quickly retort, we are expected to maintain behavioral and emotional poise. Each of these examples illustrates a situation requiring inhibitory control, a critical executive function that is broadly defined as the ability to prevent prepotent actions. Without the ability to inhibit, we would be unable to prevent ourselves from executing inappropriate responses, ignore task-irrelevant stimuli, and provide our cognitive system the time needed to exercise evaluative/regulatory functions.

Inhibitory control is a form of cognitive control, which has been identified as a construct in the Cognitive Systems domain of functioning in the RDoC framework. It involves the identification and evaluation of a conflict caused by the cross-talk of mutually exclusive responses during a task (i.e., conflict monitoring) and resolution of the conflict in a goal-directed manner (i.e., conflict resolution; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick, Cohen, & Carter, 2004).

To function adaptively in the environment, inhibitory control processes must engage in various contexts. Two contexts identified within the RDoC framework are interference control and motor inhibition. Interference control refers to the ability to resolve conflict created by task-irrelevant information when completing a task. This is commonly demonstrated in the Ericksen Flanker (EFT), Stroop, and Simon tasks. In the EFT specifically, a target arrow is flanked by two arrows on each side that are pointing in either the same (congruent; i.e., > > > > > ) or opposite (incongruent; i.e., > > < > >) direction as the target arrow. This task captures the phenomenon that participants take longer to respond on trials in which incongruent, rather than congruent, irrelevant information is presented (Nigg, 2000). It is presumed that the flankers are distracters that produce attentional competition with the target, and inhibitory control is needed to maintain goal-oriented focus (Friedman & Miyake, 2004).

Motor inhibition refers to the ability to deliberately suppress an automatic or prepotent response (Friedman & Miyake, 2004). This is commonly demonstrated in Stop-Signal and Go/No-Go tasks. In the Stop-Signal Task specifically, participants make dichotomous selections regarding a stimulus, to which they provide a response, often in the form of a button press. Due to the repetitive nature of these trials, the button press becomes the dominant response. However, on a minority of trials, a stop-signal cue is presented, simultaneously to the stimulus and at a delay, prompting the inhibition of the button press. In these situations, conflict is produced between the dominant, prepotent response and the targeted, inhibited response (Nigg, 2000).

While both interference control and motor inhibition contexts require inhibitory control to move towards the respective task goals, interference control requires inhibition primarily in the attentional domain, and motor inhibition requires control in the behavioral domain. Therefore, examining inhibitory control in both contexts provides valuable information to determine if inhibitory control is a unidimensional construct.

**Inhibitory Control-Related Brain Areas**

Neuroimaging methods of typically-developing individuals have provided valuable information about the process of inhibitory control and identified three key brain regions associated with inhibitory control processes. First, the anterior cingulate cortex (ACC) has consistently demonstrated sensitivity to experimental manipulations that require the use of inhibitory control. Specifically, the ACC shows increased activation when conflict is detected during tasks that require inhibiting attention to distracting stimuli (e.g., EFT) and inhibiting prepotent behavioral responses (e.g., Stop-Signal Task), as well as during error commission (Botvinick et al., 2001). The ACC's role appears to be evaluative, such that it detects the occurrence of a conflict but recruits other brain regions to provide resolution. Support for ACC's role in conflict evaluation is provided by studies that have manipulated the frequency of high-conflict (e.g., incongruent) trials. The ACC shows greater activation when high conflict trials are infrequent (vs. frequent), suggesting that less conflict monitoring is necessary once resolution processes have been activated (Braver, Barch, Gray, Molfese, & Snyder, 2001; Jones, Cho, Nystrom, Cohen, & Braver, 2002).

Once the ACC has identified a conflict, it signals to other regions the need for conflict resolution. In fact, cross-talk, as reflected through long-range theta coupling, has been identified between the ACC and dorsolateral prefrontal cortex (DLPFC), which is theorized to play a key role in resolving the conflict (Cavanagh, Cohen, & Allen, 2009; Mansouri, Tanaka, & Buckley, 2009). In particular, it appears that the DLPFC functions in cognitive set-shifting, as a meta-analysis found that patients with DLPFC damage had more perseverative errors in the Wisconsin Card Sort Task (WCST) than did their healthy counterparts (Demakis, 2003). In corroboration, primates with DLPFC lesions were unable to adjust their behavior to changing rules during an analog WCST. Conversely, behavior modification remained intact when an animal's ACC was lesioned but the DLPFC was preserved (Mansouri, Buckley, & Tanaka, 2007). Collectively, findings from these studies purport that the DLPFC functions in making behavior modifications following the implementation of conflicting rule changes.

The orbitofrontal cortex (OFC) also appears to respond to the ACC's signals dictating the need for conflict resolution (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). The OFC is activated during the inhibition of a prepotent "go" motor response in the Go/No-Go Task, as well as during the cessation of an already-initiated overt motor response in Stop-Signal Task (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). It is therefore thought that the OFC is specifically involved in behaviorally-focused response overrides (Altshuler et al., 2005; Horn et al., 2003).

**Behavioral and Electrophysiological Indices of Inhibitory Control**

Behavioral tasks alone produce data that is the end result of inhibitory control processes but do not offer insights into the brain activations promoting inhibitory control mechanisms. For this reason, behavioral tasks have been paired with various psychophysiological methods, allowing researchers to glean information about both the brain mechanisms subserving inhibitory control and the associated behavioral outcomes achieved.

While neuroimaging methods provide important insight into brain structures activated during inhibitory control, they are not temporally sensitive. Their methods depend on blood flow to, and deoxygenation in, the activated regions, which takes about six seconds from the time of the event (Logothetis, 2002). By offering temporal precision on the order of milliseconds, event-related potentials (ERPs) provide a valuable complement to these imaging methods. ERPs are electrophysiological measurements of summated neural electrical responses that are time-locked to task events. For this reason, they permit insight into the timing of cognitive processes that unfold in quick succession, such as the conflict monitoring and conflict resolution stages of inhibitory control. A wealth of studies have collected ERPs while participants completed inhibitory control tasks, and they have identified ERP components associated with the inhibitory control stages of conflict monitoring and conflict resolution that are present in interference control and motor inhibition contexts. Behavioral outcomes associated with these mechanisms provide an additional layer of information about inhibitory control and are also discussed.

**Behavioral Correlates of Interference Control**

Tasks of interference control frequently employ both low- (i.e., congruent) and high- (i.e., incongruent) conflict trials. While the juxtaposition of these trial types increases the probability of an error, they also allow for the examination of conflict effects through a comparison of accuracy and reaction times to low- and high- conflict trials. On high-conflict trials, response conflict is provoked and interference control is necessary to suppress the automatic response (c.f., Ridderinkhof & van der Stelt, 2000). While interference effects have been explored in high- and low- impulsivity populations, between-group differences have only been achieved when high-conflict trials are infrequent, as the level of control needed to overcome interference is high (e.g., Swick & Jovanovic, 2002; West & Alain, 2000). In contrast, interference effects have not been achieved when tasks contain comparable percentages of high- and low-conflict trials (Lansbergen, van Hell, & Kenemans, 2007).

**ERP Correlates of Interference Control**

One event-related brain potential (ERP) component, the error-related negativity (ERN), or error negativity (Ne), has been demonstrated as a neural indicator of conflict monitoring (Falkenstein, Hohnbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Researchers have most frequently studied this component through the use of conflict-ridden tasks that require inhibiting attention to distracting stimuli (e.g., EFT, Stroop task, Simon task). In these tasks, the ERN is observed as a negative-going deflection occurring approximately 50 ms after a quick, erroneous response, likely based on partial or incomplete analysis of the stimuli (Dehaene, Posner,

& Tucker, 1994). A common interpretation of the ERN, called the conflict monitoring hypothesis, suggests that continued processing of the stimuli after the erroneous slip leads to a post-error activation of the correct response, and hence conflict with the response that had been produced (Yeung, Botvinick, & Cohen, 2004). The argument for the ERN serving an indicator of conflict monitoring is augmented by consistent evidence indicating that the ACC is the neurophysiological source of the ERP component (Carter et al., 1998; Kiehl, Liddle, & Hopfinger, 2000; Miltner et al., 2003).

The ERN is followed by an error positivity (Pe) component, a positive deflection that is maximal over centro-parietal midline sites approximately 200 to 400 ms after the commission of an error. The role of the Pe remains somewhat uncertain, although the most consistent finding is that the Pe is larger on trials in which the individual is consciously aware of an erroneous response (Falkenstein, Hoorman, Christ, & Hohnsbein, 2000). Among studies corroborating this interpretation is dual-task study in which fear was induced in spider-phobic participants through the presence of a spider in the room. Relative to control trials, in which a spider was not present, spider-phobic participants demonstrated an attenuated Pe on experimental trials, suggesting reduced attentional allocation to, and salience of, their errors (Moser, Hajcak, & Simons, 2005). Other studies have found that the Pe is generated only for perceived errors (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001), which stands in contrast to the ERN, which is present across both perceived and unperceived errors (Orr & Carrasco, 2011).

Considered to be functionally distinct from conflict monitoring associated with the ERN, the Pe is purported to relate to conflict processing, such that it indexes the

salience of the error for the purpose of providing input into subsequent behavior modification to decrease the probability of subsequent errors. As such, its function may be considered an attention-based form of conflict resolution, in line with the interference control context in which it occurs. The Pe is likely a combination of frontal activation in the ACC (Bush, Luu, Posner, 2000) and a more posterior P3 response generated from activation in the superior parietal cortex (Arbel & Donchin, 2009; van Veen & Carter, 2002), providing further support for its role in attention-based conflict resolution.

Accordingly, the extent to which an error is processed, as measured by the Pe amplitude, should be correlated with behavioral adjustments on the following trial. Indeed, several studies show that only when participants were aware of their errors and exhibited a normal Pe did they evince post-error slowing (Mathalon et al., 2002; Nieuwenhuis et al., 2001). The correlational relationship between Pe and post-error slowing has been replicated in a number of studies (e.g., Hajcak, McDonald, & Simons, 2003b), but is not consistently found.

**Behavioral Correlates of Motor Inhibition**

Unlike in interference control procedures, where the accuracy rates and RTs of high- and low-conflict trials can be compared, the Go/No-Go task does not offer a behavioral measure of conflict resolution. The Go/No-Go task produces average reaction times to "go"-trials, but there is no metric to assess behavioral inhibition on "no-go"-trials. However, behavioral measures of inhibition can be ascertained from the variant procedure of the Stop-Signal Task. As described above, this procedure cues participants to make an overt response whenever a go-stimulus is presented; however, the

simultaneous presentation of stop-signals at a delay creates conflict between the already-initiated "go"-response and the "stop"-process requiring withholding of that prepotent response.

The amount of time that separates the onset of the go-signal from the onset of the stop-signal is called the stop-signal delay (SSD). Conceptually, it is easier for participants to withhold their responding when the stop-signal appears very shortly after the go-signal, and it is harder for participants to withhold their responding with an extended stop-signal delay. Therefore, in many Stop-Signal Tasks, researchers vary the SSD systematically, based on the individual's performance, to produce a successful stop rate of approximately 50% in each subject.

This systematic variation of the SSD functions in accordance with the "horse-race model," which posits that mechanisms involved in initiating a response are independent from those involved in inhibiting a response (deJong, 1990; Logan & Cowan, 1984). This model proposes that the onset of the go-signal initiates excitatory response mechanisms (i.e., horse 1), while the onset of the stop-signal initiates inhibitory mechanisms (i.e., horse 2). Therefore, a race ensues between the two processes. If the inhibitory mechanisms completes before the response mechanisms (i.e., horse 2 wins), the individual successfully inhibits the response. In contrast, if the excitatory response mechanisms complete before the inhibitory mechanisms (i.e., horse 1 wins), the response is not successfully withheld. The amount of time taken for the inhibitory mechanisms to complete their job, or in other words, the time taken to inhibit the prepotent go-response after presentation of the stop-signal, is called the stop signal reaction time. This value can

be inferred using the participant's average SSD necessary to produce ~50% successful stopping, as well as the participant's RT to go-signals (specifically, the reaction time on go-trials that is associated with ~50% successful stopping). The procedure for calculating the SSRT follows in the Methods section. Through this process, the SSRT provides an index of the efficiency of an individual's behavioral inhibition system that isn't delineated in Go/No-Go tasks. Short SSRTs are indicative of strong inhibitory control functioning, and long SSRTs are indicative of poor inhibitory control functioning.

**ERP Correlates of Motor Inhibition**

The N2 is a frontal negative-going ERP component that is sensitive to conflict. Larger N2 amplitudes have been observed during incongruent (high-conflict) relative to congruent (low-conflict) flanker (Yeung et al., 2004) and Stroop (Holmes & Pizzagalli, 2008) trials. In addition to detecting conflict caused by distracting stimuli, the N2 appears to similarly detect conflict during inhibition of a motor response. In Go/No-Go tasks, the N2, observed in the right fronto-lateral region, is larger on no-go trials, where responses are to be withheld, compared to go-trials. The same pattern frequently emerges when an individual receives indication to halt an already-started motor response (i.e., Stop-Signal Task; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004). The function of the no-go or stop-related N2 in conflict monitoring is further supported by source localization indicating that the neural generator of the N2 is the ACC (Bekker, Kenemans, & Verbaten, 2005; Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003; Yeung et al., 2004).

Temporally following the N2 in the Stop-Signal Task is a positive-going P3 component (Bokura, Yamaguchi, & Kobayashi, 2001; Roberts, Rau, Lutzenberger, & Birbaumer, 1994). Like in the Go/No-Go Task, the P3 is larger on no-go trials that require inhibition of the prepotent go-response. When responses are successfully withheld (i.e., on successful stop-trials [SSTs]), this "no-go" P3 manifests with a frontocentral midline distribution, which has been source-localized to the OFC and other prefrontal cortices (Bokura et al., 2001; Kok et al., 2004). This no-go P3 has, in fact, been compared to the novelty P3a observed in classic oddball paradigms, as novel, task-irrelevant stimuli are theorized to similarly elicit inhibitory processes (Simons, Graham, Miles, & Chen, 2001). In contrast, on trials in which the reponse is not successfully withheld (i.e., on unsuccessful stop-trials [USSTs]), the P3 appears later and has a parietal distribution and more overlapping features with the classic P3b that functions in stimulus evaluation and context updating (Donchin & Coles, 1988). Wessel and Aron (2015) confirm that the onset latency of the no-go P3 on successful stop-trials occurs in time to reflect successful motor inhibition. They also found this latency to be highly correlated (r=.60) with the SSRT.

## Differing Patterns of Inhibitory Control Dysfunction in Obsessive-Compulsive Disorder and Trichotillomania

Motivation to explore inhibitory control across repetitive behaviors is driven in large part by data indicating heterogeneity in inhibitory control patterns in obsessive-compulsive disorder (OCD) and trichotillomania (TTM). OCD is characterized by repetitive and unwanted thoughts, impulses, or images (obsessions) and behaviors rigidly

performed in response to obsessions (compulsions). TTM is characterized by excessive hairpulling that results in noticeable hair loss, often preceded by an urge, and followed by a feeling of relief, at the site of pulling (American Psychiatric Association, 2013). It is purported that OCD's rigid thought patterns and repetitive thoughts and behaviors, and TTM's hairpulling, are associated with inhibitory control dysfunction (Rapoport, 1991).

OCD and, to a lesser extent, TTM have been studied across the contexts of interference control and motor inhibition. Conceptually, examining data both across repetitive behavior presentations and across contexts permits an understanding of whether or not inhibitory control is a unidimensional construct (i.e., is the pattern of dysfunction the same across contexts or stages of control in a given disorder?), the relationship of inhibitory control among repetitive behaviors (i.e., is the pattern of dysfunction the same across presentations?), and any interactions (e.g., are patterns of dysfunction across contexts similar in certain presentations relative to others?). The differences of inhibitory control patterns across stages of control and contexts, as well as between OCD and TTM, suggest that these are important questions to extend to other repetitive behaviors before relationships can be fully understood.

**Interference Control Dysfunction in OCD and TTM**

Data consistently point to ACC hyperactivity in individuals with obsessive-compulsive presentations (Baxter et al., 1987; Ursu, Stenger, Shear, Jones, & Carter, 2003), and in fact, imaging data suggest that individuals with OCD have significantly larger ACC volumes than controls (Baer et al., 1995) with volume size correlating positively with obsession severity (Rosenberg & Keshavan, 1998). The ERN component

has also been used to explore conflict monitoring during interference control tasks. Gehring and colleagues (2000) found that the ERN is enhanced in individuals with OCD, a result that has since been well-replicated. In behavioral tasks of interference control, individuals with OCD often have poorer performance in both the color (Hartston & Swerdlow, 1999) and emotion word (Foa, Ilai, McCarthy, Shoyer, & Murdock, 1993) Stroop tasks, as well as on tasks requiring selective attention (Clayton, Richards, & Edwards, 1999). Taken together, neurobiological data find that OCD is consistently associated with heighted levels of interference control, which may contribute to impaired behavioral performance.

The relationship of the Pe to psychopathology has been less consistent in OCD, with differences that have not yet been reconciled. The Pe has been found to be larger in 10 year-old children with parent-reported OCD symptoms (Santesso, Segalowitz, & Schmidt, 2006), smaller in undergraduates with OC symptoms (Hajcak & Simons, 2002), and comparable to controls in adults with OCD (Gehring et al., 2000).

Although limited research has examined interference control in TTM, data is suggestive of reduced conflict monitoring. Whereas OCD is consistently associated with hyperactive basal ganglia (BG) functioning, which interacts heavily with the ACC, studies of TTM yield some results indicating hypoactivity of BG structures (Chamberlain et al., 2008; Fitzgerald, MacMaster, Paulson, & Rosenberg, 1999; Keuthen et al., 1996; O'Sullivan et al., 1997). Further, ERP studies of interference control have indicated either no difference (Hajcak, 2006) or decreased levels of conflict monitoring in TTM relative to controls (Roberts, Stanley, Franklin, & Simons, 2014). In both of these studies, no

relationship was found between the Pe and TTM (Hajcak, 2006; Roberts et al., 2014). Neurobehavioral testing comparing OCD and TTM found that only the OCD group demonstrated impairments in visual pattern recognition (Chamberlain, Fineberg, & Blackwell, 2007). Collectively, data suggest that OCD is associated with hyperactive conflict monitoring during interference control, whereas nascent research on TTM indicates reduced levels of conflict monitoring during interference control.

**Motor Inhibition Dysfunction in OCD and TTM**

Like the ACC, the OFC appears to be hyperactive in individuals with OCD (c.f., Friedlander & Desrocher, 2006; c.f., Saxena, Brody, Schwartz, & Baxter, 1998). Both neuroimaging and behavioral studies have indicated that OCD is associated with deficits in response suppression and motor inhibition. Specifically, they have found that OC symptom severity positively correlates with suppression errors (Cox, 1997; Rosenberg, Dick, O'Hearn, & Sweeney, 1997). OC groups have also demonstrated poorer performance than controls on a test of oculomotor suppression (Rosenberg et al., 1997) and on a goal-oriented anti-sacchade task, where they were asked to inhibit themselves from looking at novelty stimuli (Tien, Pearlson, Machlin, Bylsma, & Hoehn-Saric, 1992).

Using the Stop-Signal Task, OCD has been consistently associated with longer SSRTs than control groups (Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006), insofar as a meta-analysis has indicated a medium effect size (g=.77) for SSRT deficits for individuals with OCD (Lipszyc & Schachar, 2010). Such deficits indicate a longer amount of time needed for motor inhibition processes to complete, and hence poor inhibitory control. Interestingly, unaffected first-degree relatives of individuals with OCD

also demonstrate longer SSRTs (Chamberlain, et al., 2007).

Despite a clear pattern to the behavioral deficits associated with OCD, ERP measurements of the motor inhibition stages of conflict monitoring and conflict resolution have yielded inconsistent results. Data from a Go/No-Go Task yielded reduced no-go and go N2s in the OCD group (Kim, Kim, Yoo, & Kwon, 2007), while other data from another Go/No-Go Task (Ruchsow et al., 2007) and an auditory oddball task (Towey, et al., 1993) yielded enhanced no-go N2s in the OCD group. Inconsistencies have also been found for the no-go P3. Data from Go/No-Go Tasks have yielded smaller no-go P3s in the OCD group (Herrmann, Jacob, Unterecker, & Fallgatter, 2003; Malloy, Rasmussen, Braden, & Haier, 1989), as well as no between-group differences in no-go or go P3s (Kim et al., 2007; Ruchsow et al., 2007). Although ERP evidence is less clear, behavioral and functional imaging data suggest that OCD is associated with hyperactivity of brain structures implicated in motor inhibition, as well as poor behavioral performance on tasks of motor inhibition. Overall, the picture painted by OCD research indicates hyperactive cognitive processes associated with inhibitory control, manifesting in poorer behavioral outcomes.

There is a paucity of literature available on motor inhibition in TTM. Available studies indicate that TTM may be associated with more cognitive flexibility than OCD, such that individuals with TTM may better be able to cognitively shift from away from a go-response when a no-go- or stop-signal is presented. Interestingly, the same TTM individuals evinced significantly longer SSRTs than those with OCD, indicating relatively worse motor inhibition (Chamberlain et al., 2006). A second study using a

Go/No-Go paradigm corroborated findings that motor inhibition is more impaired in TTM than OCD, and also found earlier-onset TTM to be associated with greater deficits (Bohne, Savage, Deckersbach, Keuthen, & Wilhelm, 2008). Although there are no known neuroimaging or ERP studies of motor inhibition in TTM, behavioral data converge to suggest TTM's association with poor motor inhibition.

### Motivation for Heterogeneity of Inhibitory Control in Repetitive Behaviors

Taken together, OCD appears to have hyperactive conflict monitoring during interference control tasks, whereas TTM is associated with typical or reduced conflict monitoring in this context. Although motor inhibition has been studied more in OCD, emerging evidence with TTM suggests more deficits in motor inhibition than with OCD. The RDoC-driven question remains as to how inhibitory control dysfunction may present in other repetitive behavior presentations.

## Inhibitory Control in Tic Disorders and Autism Spectrum Disorders

Two disorders characterized by repetitive behaviors that profoundly interfere with the daily functioning of children and adolescents are tic disorders (TDs) and autism spectrum disorders (ASDs). TDs are characterized by sudden, repetitive motor movements (e.g., eye blinking, arm movements) and/or vocalizations (e.g., coughing, syllables). Individuals with either motor or vocal tics are given a diagnosis of chronic tic disorder (CTD), and those with tics in both domains are given a diagnosis of Tourette's syndrome (TS). In addition to social deficits, ASDs are characterized by restricted, repetitive patterns of behavior, which may include repetitive movements (e.g., hand flapping or finger flicking), use of objects (e.g., lining up toys or spinning coins), and

speech (e.g, stereotyped use of words or phrases; American Psychiatric Association, 2013).

TDs and ASDs, like other disorders of repetitive behaviors, present with some shared features that elucidate the limitation of categorizational diagnosis and make plausible common mechanisms of dysfunction. First, both TDs and ASDs are neurodevelopmental, such that they typically manifest early in development and are characterized by developmental deficits (American Psychiatric Association, 2013). ASDs may be recognized from as early as 1 to 2 years of age, while symptoms of TDs typically emerge between the ages of 5 and 7. Both presentations are also chronic, with severity peaking prior to adulthood. Specifically, for children with an ASD, symptoms are most marked in childhood and decrease as developmental gains are made in later childhood and adolescence. The symptoms of TDs wax and wane, but severity typically peaks in mid-adolescence and improves into adulthood (Leckman et al., 1998).

At the behavioral level, TD and ASD presentations include vocalizations like echolalia and palilalia (Robertson & Stern, 1997) and repetitive motor movements of the limbs (Canitano & Vivanti, 2007). Although perhaps due in part to symptom overlaps, the comorbidity between TDs and ASDs far exceeds chance. One study of children and adolescents with ASD found 22% to have comorbid tic diagnoses (11% CTD, 11% TS; Canitano & Vivanti, 2007). Other studies have found similar rates (8.1% TS; Baron-Cohen, Mortimore, Moriarty, Izaguire, & Robertson, 1999; 9.8% CTD, 4.0% TS; Simonoff et al., 2008). The relationship between these presentations is further bolstered

by similarly heightened rates of comorbid OCD (American Psychiatric Association, 2013).

While sharing many features, there are characteristics that distinguish the presentations. For example, the movements and utterances of TDs are distinct from those of ASD due to a preceding premonitory urge, as well as a feeling of relief once the tic is performed (Himle, Woods, Conelea, Bauer, & Rice, 2007). Individuals with ASD report neither antecedents to, nor reinforcements following, their repetitions. Further, repetitive motor behaviors in ASD encompass seemingly goal-directed actions (e.g., repeatedly walking the perimeter), whereas complex repetitive motor behaviors in TDs may involve multiple muscle groups (e.g., bending or gyrating) but are not extended to such complex actions. While some ASD motor behaviors do involve single or multiple muscle groups (e.g, hand flapping), it is notable that a number appear to be ritualistic in nature, often relating to the insistence on sameness and resistance to change (Baron-Cohen et al., 1999).

Taken together, TD and ASD overlap in simple motor and vocal repetitions, heightened comorbidity with each other and OCD, neurodevelopmental natures, and chronic trajectories with peak severities in younger years. However, given that their presentations remain somewhat heterogenous, examination of associated inhibitory control processes is necessary.

## Inhibitory Control Dysfunction in TD

***Interference control dysfunction in TD.*** Far less research has been performed on TDs than OCD. Still, it is theorized that TDs' motor and vocal symptomatology reflects

the failure of inhibitory control mechanisms. A study in which functional magnetic resonance imaging (fMRI) was used to examine cortico-striato-thalamo-cortical circuits yielded weaker activity in portions of the circuit that exert top-down control over caudate and ACC. Accordingly, activity in these regions were found to have progressively less activity (Wang et al., 2011). In concert, structural and functional studies of TDs have concentrated on the dysfunction of the BG and found both smaller BG volume and less BG activation in this population (c.f., Peterson et al., 2001). At least one study has also found decreased gray matter in the ACC of individuals with TDs (Muller-Vahl et al., 2009). On the surface, this pattern seems to contrast OCD's enlarged and hyperactivated ACC and more closely aligns with that of TTM.

Electrophysiological data demonstrate inconsistent conflict monitoring deficits associated with interference control in TDs. A preliminary study of symptomatic undergraduates (n=4) in the same lab in which the present study was conducted, used a letter version of the EFT and yielded no difference in ERN or Pe between TD and control groups. This was very recently corroborated in 8-12 year-olds with and without TD (Eichele et al., 2016). A third study found enhanced ERNs during an oddball task in adults with TD (Johannes et al., 2002). However, it was reported in the discussion that all TD participants displayed at least some OCD symptoms. Given that OCD reliably enhances ERN magnitude (Gehring et al., 2000), this makes curious the extent to which OCD symptoms contributed to the results. Interestingly, in a later study, when an OCD group was compared to an OCD group with comorbid tics, only the OCD group had significantly higher amplitude compared to controls. Individuals with comorbid OCD and

tics evinced ERNs like controls, suggesting that tic symptomatology alone may be associated with decreased levels of conflict monitoring that served to counteract OCD's reliable ERN enhancement (Hanna et al., 2012). Taken together, the data suggest that, if different from controls, TDs may be associated with reduced levels of conflict monitoring in the context of interference control. If so, TD may again align more closely with TTM, given its reduced ERN (Roberts et al., 2014).

***Motor inhibition dysfunction in TD.*** Behavioral studies have indicated that the DLPFC, but not the OFC, may be implicated in TDs. Studies of cognitive set shifting, including the WCST (Bornstein, 1990) and dual-performance tasks requiring inhibition (Baron-Cohen, Cross, Crowson, & Robertson, 1994) have found that TD groups demonstrate poorer performance than controls. In a study of individuals with comorbid OCD/TD and controls, individuals in the OCD/TD group also made significantly more errors in the Color Word Interference Test, corroborating evidence that these individuals have difficulty shifting cognitive sets to meet changing task demands. In contrast to these DLPFC-implicated tasks, studies using Go/No-Go and Stop Signal Tasks that require motor inhibition from the OFC found no differences between TD and control groups (Li, Chang, Hsu, Wang, & Ko, 2006; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008). Based on these data, it appears that shifting cognitive focus, perhaps from the go-signal to the no-go- or stop-signal may be impaired, while the overall latency of motor resolution is not impaired. Despite no behavioral differences, it is possible that groups may show different associated levels of conflict monitoring and/or resolution, evidenced through psychophysiological measures. However, at present, there

are no known ERP studies employing motor inhibition tasks in TDs, nor functional neuroimaging data, to corroborate purported behavioral deficits.

**Inhibitory Control Dysfunction in ASD**

***Interference control dysfunction in ASD*.** ASD is more consistently associated with a unidirectional pattern of deficits in conflict monitoring than is TD. Relative to asymptomatic controls, individuals with ASD evince smaller right ACC volumes, less metabolically active ACCs, and functional deactivation of the ACC during conflict detection (Agam, Joseph, Barton, & Manoach, 2010; Haznedar et al., 1997). In line with decreased ACC functioning, most studies report smaller ERNs in ASD groups than controls (Notebaert et al., 2009; South, Larson, Krauskopf, & Clawson, 2010; Vlamings, Jonkman, Hoeksma, Van Engeland, & Kemner, 2008), although some studies find no between-group differences (Groen et al., 2008). Collectively, research is suggestive of decreased functioning during interference control tasks in individuals with ASD. At the surface, this pattern of functioning appears to align with TTM and TD.

*Motor inhibition dysfunction in ASD*. Behavioral research is suggestive of deficits in conflict resolution processes. Like TD, it appears from behavioral research that cognitive control deficits in ASD lie heavily in inflexibility. In tasks requiring DLPFC implementation of cognitive set shifting, such as the WCST and Tower of London task, autism groups demonstrated more perseverative errors and deficient performance, respectively (Liss et al., 2001; Ozonoff & Jensen, 1999). Some deficits in motor inhibition, indicative of OFC dysfunction, have also been observed in a Go/No-Go Task (Ozonoff, Strayer, McMahon, & Filloux, 1994). Functional imaging research on ASDs is

nascent and has not yet focused analyses on the DLPFC or OFC. There is one known ERP study of ASD children involving conflict detection and resolution, which found that the N2 of ASD children was significantly smaller in high conflict trials that followed low conflict trials than in controls (Larson, Clawson, Clayson, & South, 2012). Taken together, data present a mixed picture, but if different from controls, it appears that ASDs are associated with poorer motor inhibition.

## Aims of the Present Research

Repetitive behaviors are a common thread among numerous psychopathological disorders and cause significant interference in daily functioning of these children and adolescents. Repetitive behaviors exhibit overlaps in comorbidity, neurobiology, phenomenology that lend to the notion that these presentations are not entirely distinct as is suggested by the present categorical approach to diagnosis. Although inhibitory control may be a common dysfunctional mechanism, evidence from OCD and TTM suggest that the pattern of dysfunction varies across presentations, and perhaps across stages of control and contexts. Overcoming categorical limitations, the proposed study is in line with the RDoC initiative and integrates ERPs, behavioral measures, and observable symptoms to examine inhibitory control dysfunction in two repetitive behaviors. The goal is to determine if the patterns of inhibitory control dysfunction found in OCD and TTM extend TDs and ASDs.

Understanding the relationships among repetitive behaviors, particularly by integrating neuroscience with observable symptoms, is a critical step in restructuring our diagnostic system structure so that it may provide meaningful diagnoses. It is also

important to treatment in two key ways. First, it will encourage the refinement of treatments for repetitive disorders to ensure direct targeting of the mechanism of dysfunction. It will also aid in treatment planning, such that if the repetitive behavior is not the core interfering symptom targeted in treatment, modules targeting the associated mechanism of dysfunction can be incorporated into treatment. Second, research on the neurobiology associated with some complex repetitive behavior presentations, like ASDs, is still nascent. Understanding the relationship of ASD to other repetitive behaviors, of which there is greater understanding, may provide insights into common neural correlates that could propel research.

In an effort to overcome categorical boundaries, as proposed by the RDoC initiative, and due to the particular overlap between TDs and ASDs relative to other repetitive behaviors, the proposed study will investigate TDs and ASDs as a single group of repetitive behaviors (i.e., the RB group). Evidence of inhibitory control dysfunctions in these populations, similar to those seen in OCD and TTM, provides motivation to investigate whether or not TDs and ASDs demonstrate similar abnormalities. To date, psychophysiological studies of these repetitive behaviors have demonstrated somewhat inconsistent findings. Albin and Mink (2006) suggest that inconsistent results are largely due to heterogeneity within the groups. One such reason is the inclusion of individuals with comorbid diagnoses that are associated with dysfunction in inhibitory control, such as OCD (Albin & Mink, 2006). By excluding individuals with comorbid OCD, the hope was to prevent the between-group interpretative difficulties encountered in many previous studies. Further, by capitalizing on the temporal precision of EEG, the conflict

monitoring and conflict resolution stages of inhibitory can be compared across contexts, and information can gleaned about the specificity of any deficits for the neurodevelopmental RB group across stages of control (i.e., conflict monitoring, conflict resolution) and the contexts in which control is taxed (i.e., interference control, motor inhibition). Therefore, the present study can identify common and/or distinct indicators of inhibitory control dysfunction in the targeted RBs.

**Aim 1: Identify Indicators of Interference Control Problems in Neurodevelopmental RBs**

As presented above, some studies have explored EEG correlates of conflict monitoring in the context of distracters. Although the results are not entirely consistent, data from structural and functional imaging, behavioral studies, and ERP studies have made plausible that both repetitive behavior presentations are associated with decreased levels of conflict monitoring relative to controls. The proposed study targeted conflict monitoring in the context of distracters by using a standard interference control task (EFT). This speeded reaction-time task required that attention be maintained on the target, despite the presence of interfering distracter arrows. Erroneous responses elicited the ERN and Pe components, the mean amplitudes of which were calculated to assess the level of conflict monitoring and conflict resolution, respectively.

It was hypothesized that the RB group would have smaller ERNs than the TDC group, reflective of decreased conflict monitoring. As outlined above, individuals with ASD exhibit behavioral deficits, structural abnormalities in the ACC, deactivation of the ACC, and fairly consistent reductions in ERN amplitudes in previously performed

experiments. Although limited data is available for the TD group, available data would also suggest decreased levels of functioning in the context of distracters due to poor conflict monitoring in behavioral tasks, BG impairments, and ACC structural deficits.

The Pe appears to provide valuable information about the awareness or salience of the salience, perhaps for the purpose of aiding in the processing and resolution of the conflict (Falkenstein et al., 2000; Moser et al., 2005). However, no predictions were made about the relationship of Pe to repetitive behaviors because of its inconsistent relationship to individual difference variables in previous studies. Further, due to the similar percentages of high- and low-conflict conditions in the EFT, no between-group differences were expected in RT or accuracy to congruent and incongruent trials.

**Aim 2: Identify Indicators of Motor Inhibition Problems in Neurodevelopmental RBs.**

Psychophysiological correlates of motor inhibition have not been extensively studied in the targeted repetitive behavior presentations. Both presentations exhibit motor and vocal symptomatology, which, coupled with evidence of atypical DLPFC and OFC functioning and deficits in behavioral studies, necessitate research into inhibitory control in the context of motor inhibition. The proposed study used the Stop Signal Task, which permitted both the conflict monitoring and conflict resolution stages of inhibitory control to be examined during motor inhibition. In this task, participants executed a speeded, dichotomous response to the direction of an arrow (i.e., go-signal); however, on one-third of trials, a cue (i.e., stop-signal; indicates a stop-trial) is presented at a varying delay after arrow presentation to signal that the participant should inhibit his/her responding.

ERPs time-locked to the stop-signal evince reliable N2 and P3 waveforms that allow for an examination of the evaluative and regulative sequential stages of the inhibitory control process, respectively. One conceptualization of the coordination of these two processes is the "Flag and Brake" model (Kok, 1986). Evidenced to reflect ACC activation, the N2 serves as the "flag" that signals the need for the onset of inhibitory processes. The no-go, frontal P3 then serves as the "brake" in accordance with Polich's neuroinhibition model of the P3a (Polich, 2007), reflecting the success or strength of the inhibitory process' motor response conflict resolution.

Thus, studying Stop-Signal Task ERPs in individuals with repetitive behaviors allowed for the determination of the extent to which inhibitory control is impaired in the context of motor inhibition. It was hypothesized that the RB group will have smaller N2 magnitudes to USSTs than the TDC group, suggesting attenuated detection of conflict. While comparable motor inhibition tasks, that are coupled with ERP recordings, have not yet been employed to study ASD or TD, individuals with ASD evince deficits in Go/No-Go Tasks of inhibition, smaller ERNs in other conflict monitoring situations, and have ACC functional deactivation during conflict detection. Similarly, individuals with TD have demonstrated dysfunction of the BG, as well as possible structural deficits in the ACC. Data is also limited for OFC and DLPFC functioning in ASDs and TDs, although some studies have shown decreased DLPFC volume and deficits on behavior inhibition tasks. Therefore, it was expected that the RB group would exhibit decreased no-go P3 amplitudes.

With regard to the SSRT, it was hypothesized that the RB group would have longer latencies than the TDC group, due to poor performance on motor inhibition tasks and symptomatic inflexibility in individuals with ASD, and no difference to poorer performance on inhibition tasks in individuals with TDs.

# Chapter 2

# METHOD

## Participants

Seventy-six individuals between the ages of 8 and 17 years old served as participants. Of these, 43 carried diagnoses of disorders characterized by repetitive behaviors (33 ASD, 10 TD), and 33 had no psychological diagnoses. Of participants comprising the repetitive behavior (RB) group, 11 (25.6%) reported a comorbid anxiety disorder diagnosis and 13 (30.2%) reported a comorbid ADHD diagnosis. Participants were recruited from research and treatment centers specializing in their targeted disorder (e.g., ASD: Center for Autism Research [CAR] at the Children's Hospital of Philadelphia; TD: Child and Adolescent OCD, Tic, Trichotillomania, and Anxiety Group [COTTAGe] at the University of Pennsylvania), psychologists, psychiatrists, and neurologists in the greater Philadelphia area, the Tourette Syndrome Associations of New Jersey and Pennsylvania, as well as local support groups and events.

### Eligibility

Individuals interested in the study completed a two-phase screening process to establish if they met all inclusion and no exclusion criteria. A phone screener was administered to determine most eligibility requirements. If participants met these eligibility requirements, they were administered an in-person cognitive assessment.

***Phone screener.*** A parent of each participant completed a phone screener, which included details about the child's diagnoses. Participants met diagnostic eligibility for the experimental group if they carried a current diagnosis of one of the targeted repetitive behavior disorders (TD or ASD). Individuals with TD recruited from COTTAGe (n=4) had received their diagnosis through clinical interview employing the Yale Global Tic Severity Scale. Those with TD recruited from community sources were diagnosed through clinical interview, frequently without use of standardized measurement tools. Individuals with ASD were recruited through a database of children and adolescents who had previously completed neuroimaging research at CAR and were willing to be contacted about future studies. As part of their previous research, each had been administered the ADOS for confirmation of their diagnoses.

Participants eligible for inclusion did not have a comorbid diagnosis, nor a parent-reported history of comorbid symptoms during the screener, of any other repetitive behavior disorders (e.g., the other targeted disorder, TTM, OCD) or psychosis. Exclusions for comorbid TTM and OCD were due to known effects on ERP modulation in these components that may confound data due to their higher rates of prevalence in individuals with other RBs. Individuals in the TDC group were excluded for delays suggestive of ASD-like impairment, Axis I or psychiatric disorders (e.g., psychosis, affective, anxiety, or conduct disorders) or use of medication to treat such symptoms. Individuals with ASD and TD were eligible if they had not yet started treatment, or if they were involved in treatment but still symptomatic.

Children were excluded for mental retardation, genetic or neurological conditions apart from TD, and seizure disorders that would preclude the use of EEG due to excessive movement. Individuals with allergies, skin conditions, or aversions to being touched were excluded for safety with regards to EEG electrode application. Individuals with visual disorders that could not be corrected through the use of corrective lenses to a level of 20-40 inches in both eyes were excluded because of the visual nature of these tasks. Further, individuals on neuroleptic medications (e.g., clonidine, haloperidol) were excluded due to data suggesting that they impact the ERP components targeted in this experiment (Condray, Siegle, Cohen, van Kammen, & Steinhauer, 2003; Swick, Pineda, & Foote, 1994).

***Cognitive evaluation.*** Children who met inclusion criteria based on the phone screener were brought in for a cognitive evaluation. As it was expected that groups would differ in verbal cognitive abilities, and the ERP tasks in this protocol did not require verbal acuity, the Raven Progressive Matrices (Raven & Raven, 2003) was administered to assess nonverbal intelligence. This assessment asked participants to identify, from a multiple-choice selection, the missing element of a larger pattern. Because of its nonverbal nature, Raven Progressive Matrices was selected to be assessable to children and adolescents in all groups.

Although manualized normative comparisons are not available for the Raven's Progressive Matrices, a number of standardization studies have been conducted in geographically distinct regions internationally to identify percentile equivalents for their given population. The most detailed available publicly is that a 1979 nationwide British

standardization sample (Raven, 2000), which is highly correlated with smaller samples of data collected in the United States between 1984 and 1987 (Raven, 1989). As more recent standardizations were not available, the 1979 normative table was used to generate percentiles for each subject, which were then converted into T-scores for comparison among participants of various ages. There are clear, inherent limitations of this method, most notably that the children in the present study are completing the task 46 to 47 years after the standardization data was collected. For this reason, the generational increase in cognitive scores must be given due consideration, such that scores will likely appear elevated relative to what they might be if a current standardization had been available for use (i.e., Flynn effect; Flynn, 1984).

So as to ensure the ability to understand of the experimental paradigm, those scoring below T=37 (equivalent to a standard score of 80, indicating at least *below average* nonverbal intelligence) were not eligible for inclusion in the study. Those who met inclusion criteria completed ERP tasks in the same in-person session.

**Compensation**

Participants were not compensated for completing the phone screener, nor for attending the appointment but electing not to consent. Participants who completed the study in full were paid $50 for their participation. Participants who began, but were unable or unwilling to complete, the study were compensated at the rate of $10 per hour.

## Tasks

### Flanker Task

The EFT was administered using Presentation software (Neurobehavioral Systems, Inc.), which controlled the presentation and timing of all stimuli, the identification of responses, and the measurement of reaction times. During the task, participants were shown horizontal sequences of arrows in the center of the monitor. All arrows were presented in white font on a black background. Participants were instructed to identify the direction of a center arrow, flanked by two arrows on each side. Because the flankers were either pointing the same or opposing direction as the center arrow, there were both low-conflict, congruent conditions (i.e., > > > > >; < < < < <) and high-conflict, incongruent conditions (i.e., > > < > >; < < > < <).

Following practice trials, participants completed 300 trials, divided into 6 blocks of 50 trials. Stimuli were presented randomly, such that 50% of trials were congruent and 50% were incongruent. For each trial, arrows were presented at the center of the computer screen for 135 ms, and participants responded to the direction of the center error by pressing the left or right buttons on a Cedrus button box.

### Stop-Signal Task

The Stop-Signal Task required participants to either respond to a stimulus (go-trials) or inhibit that ongoing response when a stop-signal was presented (stop-trials). The stimulus was a single arrow, pointing to either the right or left, and participants were asked to press a button corresponding to the direction of the arrow. On approximately

one-third of all trials, a red circle appeared superimposed onto the stimulus at a delay, signaling participants to inhibit their response on that trial.

The amount of time that elapsed between the onset of the go-signal (arrow) and the stop-signal (red circle) varied for each stop-trial. The initial SSD was 200 ms. When participants successfully inhibited their response, the stop-signal appeared 50 ms later on the next stop-trial. When participants did not successfully inhibit their response, the stop-signal appeared 50 ms earlier on the next stop trial. Limits were set so that stop-signal delays were no shorter than 50 ms and no longer than 1200 ms. This adaptive tracking system was designed to elicit 50% overall accuracy for each participant on stop-trials (Logan & Cowan, 1984). The stop-signal delay at which an individual achieved this accuracy was used to compute the SSRT.

Following practice trials, participants completed 240 trials, divided into 4 blocks of 60 trials. Participants were instructed to respond as quickly and accurately as possible to both the go- and stop-signals, and to not intentionally delay their responses in anticipation of a stop-signal. Participants had 1000 ms to make their response on go-trials, and they had 1000 ms plus the length of the delay to make their response on stop-trials, before the stimulus disappeared.

## Questionnaire Measures

Three questionnaires were administered to parents of all participants in order to assess the child's or adolescent's executive function, pubertal development, and ADHD symptoms. In addition, parents were asked to complete one questionnaire specific to

his/her child's diagnosis to assess the current levels of severity and interference caused by the repetitive behavior. All questionnaires were administered by pencil and paper.

***Behavior Rating Inventory of Executive Function (BRIEF).*** Executive functioning was assessed with the BRIEF (Gioia, 2000), for which a parent responded to 86 questions rating the child on everyday behaviors and skills responsible for guiding, directing, and managing his/her cognitive, emotional, and behavioral functioning. Principle components analysis has identified eight sub-domains of executive functioning, grouped into two composites, the Behavioral Regulation Index and the Metacognition Index, which are combined to obtain a Global Executive Composite score.

The BRIEF has demonstrated excellent internal consistency, ranging from $\alpha$=.80 to .98 (Gioia, Isquith, Guy, & Kenworthy, 2000). Reliability tests indicate 2-3 week test-retest reliability for BRI, MCI, and GEC is .84-.88 in typically developing children and .80-.83 in children scoring in the clinical range. Composite and some clinical scales on the BRIEF have strong concurrent and predictive validities with ADHD and its subtypes, and preliminary studies demonstrate that the BRIEF may have clinical utility in identifying other clinical presentations with dysfunction in fronto-striatal circuitry, including TDs (Mahone et al., 2002) and ASDs (Gioia, Isquith, Kenworthy, & Barton, 2002).

***Conners' Parent Rating Scale – Revised (CPRS-R).*** The CPRS-R (Conners, 1997) is a 57-item questionnaire to assess behaviors and other concerns for children between the ages of 6 and 18. Parents are asked about their child's inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, and peer

relations. The CPRS-R was used in the present study to assess for ADHD symptoms. Internal reliability ranges from α=.75-.94 for males and α=.75-.93 for females. Sensitivity is 92.3%, specificity is 94.5%, positive predictive power is 94.4%, and negative predictive power is 92.5%, all lending to an overall correct classification rate of 93.4% for ADHD (Conners, Sitarenos, Parker, & Epstein, 1998).

***Spence Children's Anxiety Scale (SCAS).*** The SCAS (Spence, 1999) is a 38-item parent-report measure, designed to measure symptoms of six DSM-IV anxiety disorders: panic disorder, generalized anxiety disorder, social phobia, separation anxiety disorder, OCD, and specific phobias. As norms for these measures do not currently exist, raw scores were used. Subscales have satisfactory to excellent internal consistency (α=.58-.81), and the total score indicated strong internal homogeneity in both anxious and control samples (α=.89). In terms of discriminant validity, the SCAS correctly identified 80.5% for the presence of an anxiety disorder. Those in the anxiety group were correctly classified 51.7% of the time, with most accurate classification occurring for the subscale of OCD (72% accuracy; Nauta et al., 2004).

***Pubertal Development Scale (PDS).*** Because of distinct developmental differences in children between the ages of 8 and 17, we administered PDS (Peterson, Crockett, Richards, & Boxer, 1988) to assess level of pubertal development. The PDS is a 5-item, parent-report measure assessing pubertal change. Parents were asked to report on five physical characteristics of their child: growth spurt, pubic hair, and skin change, as well as facial hair growth and voice change in males, and breast development and menarche in females. An overall pubertal development score is computed from the sum

of the ordinal response items. Internal consistency (α=.68-.83) and convergent validity with physician ratings (*r*=.61-.67) are satisfactory.

***Parent Tic Questionnaire (PTQ).*** The PTQ (Chang, Himle, Tucker, Woods, & Piacentini, 2009) is a 28-item measure assessing the presence, frequency and intensity of motor and phonic tics in the respondent's child over the past week. The PTQ produces a total motor tic severity score and a total vocal tic severity score that are combined for a total tic severity score. The PTQ has high internal consistency (α=.86-.90) and external 2-week test-retest reliability (ICC=.84). It also has strong convergent validity with the Yale Global Tic Severity Scale (YGTSS; *r*=.72) for total tic severity scores, even after controlling for obsessive-compulsive symptoms and inattention (*r*=.62-.65).

***Repetitive Behavior Scale – Revised (RBS-R).*** The RBS-R (Bodfish, Symons, Parker & Lewis, 2000) is a 43-item measure that aims to capture severity of repetitive behaviors associated with ASDs. It contains six conceptually-derived scales: stereotyped behavior, self-injurious behavior, compulsive behavior, routine behavior, sameness behavior, and restricted behavior. Two independent validation studies have suggested a five-factor structure that combines the routine and sameness categories. Internal consistency of subscales in the five-factor structure is high (α=.78-.91; Lam & Aman, 2006; α=.72-.89, Mirenda et al., 2010), and it has been found to correlate highly with the repetitive behavior scores on the Autism Diagnostic Interview - Revised (Mirenda et al, 2010).

***Social Responsiveness Scale (SRS).*** The SRS (Constantino & Gruber, 2007) is a 65-item measure that captures interpersonal behaviors, communication difficulties, and

repetitive/stereotypic behaviors that are characteristic of ASD. This parent-report measure produces five subscales: social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Internal consistency of parent-rating scales is strong (α=.93-.94), and test-retest reliability ranges from α=.77 in females to α=.85 in males (Constantino & Gruber, 2007). Parent-reported SRS scores demonstrated strong correlations to scores on the gold standard Autism Diagnostic Interview – Revised (*r*=.65-.77; Constantino et al., 2003).

***DSM-Oriented Questionnaires.*** To supplement disorder-specific scales and obtain a more comprehensive picture of the diagnosis-specific difficulties of individuals with ASD or TD, parents completed a DSM-oriented questionnaire specific to the diagnostic presentation, both of which were designed by the researcher. Both the ASD and TD questionnaires included questions to assess the age of symptom onset, the chronicity of the symptoms, and the level of distress/impairment caused by the symptoms across home, school, and social contexts. As the types of tics, and their frequencies and intensities, were assessed in the PTQ for individuals with TD, these were not included in DSM-oriented questionnaire. In contrast, the SRS and RBS-R do clearly access each of the DSM-V criteria for ASD, so these were included as a checklist in which parents indicated if they are a current, or were a past, difficulty across home, school, and social contexts.

## Procedure

After describing and answering questions about the study, the experimenter provided parents with informed consent form, and the child with child assent form. If the

families consented to participate, the parent was provided with copies of the relevant questionnaires to complete, and the child completed the Raven's Progressive Matrices.

The child was then introduced to EEG equipment and seated in a comfortable chair about 80 cm in front of the computer monitor. EEG sensors were attached. The child first completed a resting-state EEG task, which was not within the scope of this study and will not be further discussed in the present manuscript.

The child was then given detailed task instructions for the EFT, practiced identifying the directions of arrows using screen print-outs, and then completed two practice blocks. The child was instructed to place equal emphasis on speed and accuracy in his/her responding. The child then completed the experimental blocks. As the experimenter initiated each block, the participant was given a break between each trial block (approximately every 2-3 minutes). As needed, the experiment paused the task to allow for additional breaks.

Following completion of the EFT and an extended break, the child completed the SSRT task. The participant was given detailed task instructions, practiced identifying the directions of arrows and when to inhibit responses using printouts, and completed two practice blocks prior to beginning experimental blocks. The child was instructed to respond while the arrow stimulus was on the screen and not wait to see if a stop-signal would appear. Breaks were given at the end of each block (every 3-4 minutes) and within each block as needed.

## Psychophysiological Recording and Data Reduction

EEG were recorded from 64 silver/silver chloride (Ag/AgCl) electrodes embedded in an electrode cap with an average reference and parietal-occipital ground. Impedences were kept below 20 KΩ, and data were digitized at 512 Hz using 'ActiveTwo' hardware (Biosemi, Amsterdam, Netherlands). This active electrode system allowed for fast application and minimal discomfort for child participants, particularly those with sensory sensitivities. The onset of arrows and overt responses were time-stamped to the EFT EEG data, and the onset of arrows, stop-signals, and overt responses were time-stamped to the SSRT EEG data.

### EFT Data Reduction

Offline, continuous EEG were corrected for eye blinks, re-referenced to the average of the mastoids, and band-pass filtered from 0.1 to 30 Hz with BESA software (MEGIS Software GmbH, Gräfelfing, Germany). From the continuous files, epochs were extracted from 400 ms before to 1000 ms after the response for each trial. Trials were excluded if the response occurred within the first 100 ms following, or 1000 ms or more after, stimulus presentation. Further, trials in which artifacts exceeded a threshold of ±75 μV were automatically rejected. ERPs were then constructed by separately averaging trials for error and correct responses. For each ERP, activity in the -300 to -100 ms window prior to the response served as the baseline because it is the period of greatest stability preceding the negative deflection that begins with response selection.

Primary regions of interest (ROIs), in which the ERN and Pe components were statistically analyzed, were chosen according to literature localizing these components

(Dehaene et al., 1994; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004) and confirmed through topographic head plots (see Figure 1). Fronto-central electrodes of maximal activation formed for the ROI for the ERN, and slightly more posterior electrodes formed the ROI for the Pe. ERPs of the respective electrodes were averaged together, and mean amplitudes of the averaged ERP for the ROI were calculated during time windows consistent with component latency and previous literature (ERN: 0-100 ms; Pe: 100-300 ms).

Due to observed, developmentally-driven differences in the latency of the ERN, a second set of exploratory analyses were conducted to align trials with respect to the evoked responses using a version of the Woody Filter technique (Woody, 1967) that has been adapted for use with the ERN (Lin, Gavin, & Davies, 2015). Continuous EEG data, which had been eye-blink corrected, and rereferenced in BESA (MEGIS Software GmbH, Gräfelfing, Germany), were imported into Matlab, where the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) was used for further pre-processing.

Epochs were first extracted from the continuous EEG file from -2000 ms before to 2000 ms after the response, although trials were excluded if a button press was not made within 1000 ms of stimulus presentation. Artifact rejection was twofold, such that data were first processed for large fluctuations and then for muscle artifacts. For jump detection, within-trial data were averaged across channels. Data points were transformed into z-scores, and trials with z-score differences that exceeded ±30 were excluded from further analysis. Artifact detection was then performed by band-pass filtering data from 110 to 140 Hz to identify muscle activity, transforming data values into z-scores, and

rejecting trials with z-scores that exceed a threshold of ±5. Data were baseline corrected from -300 to -100 ms and band-pass filtered from 0.1 to 30 Hz.

For each electrode and condition, an average ERP was created, with the 0 to 300 ms window following the response serving as a template. This template was run across individual trials from -300 to 300 ms to determine the time points associated with the maximum correlation between the template and individual trial data. The data were then shifted so that, for each trial, 0 ms indicated the time of the start of the template at which the data were most highly correlated with the individual's average evoked response. ERPs were constructed by separately averaging trials for error and correct responses.

**SSRT Calculation**

The SSRT, or a calculation reflecting the length of time taken for an individual to inhibit an already-initiated motor response, is an estimate of the efficiency of that individual's inhibitory process. As EEG data reduction for the stop-signal task is contingent on obtaining an SSRT value for each participant, behavioral analysis preceded EEG analysis. Behavioral data was analyzed using a method consistent with the "horse-race" model of the stop signal task, which asserts that the stop- and go-processes compete for the first finishing time on stop-trials (Logan et al., 1997).

The calculation of each participant's SSRT required first obtaining several other calculations. First, each participant's stop accuracy (i.e., successful stop rate) was calculated by dividing the number of successful stops by the total number of stops. Across all participants, the average stop accuracy was 51.8% (*SD*: 5.6%), indicating that the tracking procedure was successful in making adjustments in the SSD based on

performance to yield a stop accuracy of approximately 50%. This value has critical utility in that it can be mapped onto the go-RT distribution for the purpose of drawing conclusions about the timings at which inhibitory processes yield successful stops versus unsuccessful stops, as will be detailed later in this section.

Next, the average SSD (i.e., on stop-trials, the average amount of time that elapsed between the onset of the go-signal and the onset of the stop-signal) was determined by averaging the delays across all stop-trials. Whereas the presentation of the go-signal initiates the excitatory response mechanism, the average SSD denotes the point in time at which the average stop-signal appears to initiate the inhibitory mechanisms. The average SSD is critical in the calculation of the SSRT. As the SSRT captures the speed of the inhibitory process, it is essential to know the time point at which these processes begin.

The third value necessary in the calculation of the SSRT is the time point by which the inhibitory processes must finish to yield successful stops. In order to obtain this value, reaction times to go-trials (i.e., trials during which a stop-signal did not appear) were rank-ordered[1]. This provided a distribution of each participant's RTs. As this entire distribution is not available for stop-trials (i.e., due to successful inhibition of some responses), the go-RT distribution is critical because it provides the individual's RT repertoire, which can then be used to draw inferences about the timings at which inhibitory processes finish to yield successful stops. Specifically, the RT associated with the position on this distribution that reflected the participant's successful stop rate (i.e.,

[1] Go-trials on which a participant did not respond (i.e., omits) were not included in this calculation. Descriptives on omissions can be found in Table 8.

the position resulting from multiplying the participant's successful stop rate by the number of go-trials) was selected as the time point for separating go-trials into "fast" (i.e., response times shorter than this value) and "slow" (i.e., response times longer than this value) categories. In other words, the mapping of the successful stop rate onto the go-RT distribution permitted determination of fast-go RTs, analogous to which trials would have been unsuccessful stops had a stop-signal been present on those trials, and slow-go RTs, analogous to which trials would have been successful stops in the presence of a stop-signal. This mapping of the successful stop rate onto the individual's go-RT distribution allowed for an inference of the average time at which each individual's inhibitory processes completed.

The SSRT was then calculated by subtracting the average SSD from this midpoint go-trial reaction time, indicating the amount of time taken for the participant to complete the inhibitory process in the midst of an already initiated go-process.

**Stop-Signal Task Data Reduction**

Offline, continuous EEG were corrected for eye blinks, re-referenced to the average of the mastoids, and band-pass filtered from 0.1 to 30 Hz with BESA software (MEGIS Software GmbH, Gräfelfing, Germany). Data were epoched to create four types of ERPs, from which two target ERPs could be constructed. The target ERPs were time-locked to the onset of stop-signals (i.e., the start of the inhibitory process): one ERP for successful stops and one ERP for unsuccessful stops. However, because of contamination by overlapping ERP activity locked to the preceding go-signal, it was necessary to first

derive ERPs for the go-signals so that they could be subtracted out from the ERPs to the stop-signals.

In doing so, two issues were taken into consideration. First, ERPs elicited by go-signals are theoretically different between fast and slow responses. The race model indicates that slower reaction times should be associated with successful stopping, and faster reaction times should be associated with unsuccessful stopping (Logan & Cowan, 1984). Therefore, in calculating the SSRT, go-trials responses were categorized "fast" and "slow" depending on if the response time was shorter or longer than the midpoint reaction time, as described above. Because of the theoretical differences, "fast-go" ERPs were used with unsuccessful stop ERPs, and "slow-go" ERPs were used with successful stop ERPs.

A second consideration was that the delay of the stop-signal for successful and unsuccessful trials varies in relation to the onset of the go-signal, such that delays for successful stops were shorter than delays for unsuccessful stops. This indicates that the two categories of stop-signal-locked ERPs would overlap with different segments of the preceding go-signal ERP. Therefore, an earlier segment of the slow-go ERP, beginning at the time point of the average stop-signal delay for successful stop-trials and continuing 1000 ms, was used for the subtraction process with successful stop-signal-locked ERPs. A later segment of the fast-go ERP, beginning at the time point indicated by the average stop-signal delay for unsuccessful stop trials and continuing 1000 ms, was used for the subtraction process with unsuccessful stop-signal-locked ERPs. ERPs were baseline corrected using the data in the -200 to 0 ms time window.

To complete the subtraction, the delay-indicated slow- and fast-go ERPs described in the previous paragraph were subtracted from the stop-locked successful and unsuccessful ERPs, respectively. This produced a successful stop-trial ERP (SST) and an unsuccessful stop-trial ERP (USST).

ROIs, in which the N2 and P3 components were statistically analyzed, were chosen according to headplots and literature localizing these components (Dehaene et al., 1994; Herrmann et al., 2004). The ERPs of the respective electrodes were averaged together to quantify each component. Consistent with literature, headplots revealed a lateralized, anterior N2 distribution, so data were analyzed at analogous ROIs in the right and left hemispheres. Data also revealed that P3 profiles differed based on successful vs. unsuccessful trials, such that the frontal, no-go P3 for SSTs occurred earlier and was more frontally distributed, and the P3 for USSTs occurred later and was more posterior to the earlier P3 effect. As a result, P3 data were analyzed at a frontal ROI with an earlier time window, and at a more posterior ROI with a later time window.

## Statistical Analyses

Questionnaire scores, performance measures, and ERP component mean amplitudes were statistically evaluated in SPSS Statistics (Version 22). Questionnaire and performance measures were analyzed by repeated-measures analysis of variance (ANOVAs), one-way ANOVAs, or *t*-tests as necessary. Using General Linear Model software, repeated-measures ANOVAs were performed separately for each psychophysiological component with group (RB, TDC) or age (8-9, 10-11, 12-13, 14-15, 16-17) as the between-subjects factor and trial type (error, correct) or success (SST,

USST) as the within-subject factor. The Greenhouse–Geisser method was applied to *p*-values to account for violations to the ANOVA assumption of sphericity.

# Chapter 3

# RESULTS

## Task 1: Interference Control

### Participants

Of the 76 participants who attended the experiment, one fainted during EEG electrode application and did not complete the EEG portions of the task, resulting in 75 individuals who completed the EFT. Data from nineteen subjects (25.3%) were excluded prior to analyses: 9 for excessive movement yielding too few usable trials, 7 for excessive (over 40%) errors, 1 for too few (<6) errors, and 2 for equipment malfunction. Thus, the final sample consisted of 56 participants: 30 RB (26 male) and 26 TDC (25 male). The mean ages of the RB and TDC groups were 13.3 (*SD*: 2.2) and 13.2 (*SD*: 2.5), with mean pubertal developmental scores of 12.4 (*SD*: 4.1) and 11.5 (*SD*: 4.1), respectively. Chi-square analysis indicated that the groups did not differ significantly in terms of gender, $\chi^2(1)=1.54$, $p=.21$. One-way ANOVAs with 2 between-group levels indicated neither age, nor pubertal development, differed as a function of group status, $F$s$(1,54)<1$.

### Psychological Profiles of Participants

Table 1 presents the psychological characteristics of the sample, including *t*-statistics and *p*-values for between-group comparisons. On the Raven's Progressive Matrices, the TDC group demonstrated significantly higher nonverbal intelligence than

the RB group, $t(54)=3.04$, $p=.004$. Parent-report questionnaires indicated that the RB group had significantly higher levels of psychopathology across all measured internalizing and externalizing domains (CBCL), behavior regulation and metacognitive executive functions (BRIEF), inattention and hyperactivity/impulsivity (CPRS-R), and anxiety (SCAS).

Disorder-specific symptomatology for those participants with repetitive behaviors is reported in Tables 2 and 3 and confirmed that participants continue to qualify for their previously-diagnosed disorder. The ASD sample endorsed a *severe* overall level of social deficits (SRS; Criterion A), falling in the *severe* range for autistic mannerisms and in the *mild to moderate* range for social awareness, social cognition, social communication, and social motivation. To meet Criterion B, the individual must have either current or past RBs in *two* of the following domains: stereotyped/repetitive motor movements, insistence on sameness, highly restricted interests, and hyper-/hypo-sensitivity to sensory input. The present participants endorsed an average of 12.3 (*SD*: 8.2) repetitive behaviors (RBS-R) within these categories, which most often fell into the categories of stereotyped/repetitive, ritualistic, and sameness behaviors. On average, for individuals with ASD, symptoms were first noticed at 2.9 (*SD*: 1.3) years old, reflecting symptom onset in early development (Criterion C).

For individuals with TD, at least one tic must be endorsed to meet Criterion A. Individuals with TD endorsed an average of 5.1 (*SD*: 2.4) tics, which were more often motor than vocal (PTQ), and tics occurred with a *mild*-to-*moderate* frequency and level

of cumulative interference. Mean symptom onset was 5.7 (*SD*: 3.9) years old, reflecting both the longstanding presence of tics and their development prior to 21 years-old.

Across all RBs, parent-reported impairment levels fell in the *moderate* range overall in three domains of functioning. Participants with ASD did not significantly differ from those with TD in disorder-related impairments at home, $t(28)=-1.06$, $p=.298$, and at school, $t(28)=1.02$, $p=.315$. ASD was associated with a marginally nonsignificant higher level of interference in social settings, $t(10.329^2)=2.16$, $p=.056$.

The psychological characteristics of included and excluded participants were then compared to determine if the subset included in analyses was representative of the larger sample. Accordingly, independent *t*-tests were conducted, such that included participants for each group were compared to excluded participants in that group, across each measured psychological characteristic. Overall, results revealed that included participants were largely similar to those excluded, as there were no differences on any index or subscale measures on the CBCL, BRIEF, and CPRS-R for either group, but that the RB group may represent a subset of the recruited sample with slightly lower, but still clinical, levels of disorder-specific psychopathology. Specifically, relative to excluded individuals with their specific RB, those included with TD endorsed fewer tics, $t(8)=-2.308$, $p=.050$, and those included with ASD endorsed fewer sameness behaviors, $t(31)=-2.701$, $p=.011$, fewer restricted behaviors, $t(31)=-2.682$, $p=.012$, and less interference caused by sameness behaviors, $t(31)=-2.068$, $p=.047$. Included versus excluded TDC participants

[2] Levene's Test of Equality of Variance indicated that equal variances should not be assumed.

differed only on one subscale of the SCAS, panic/agoraphobia, $t(25)=2.573$, $p=.016$[3], such that included TDC participants endorsed a higher level of symptomatology than those excluded; however, symptoms were within the *typical* range for both sets of TDC participants.

[3] Levene's Test of Equality of Variance indicated that equal variances should not be assumed.

Table 1

*Psychological Profiles of Participants by Group in the EFT*

| | RB | TDC | *t*-statistic | *p*-value |
|---|---|---|---|---|
| Raven's Progressive Matrices | | | | |
| Nonverbal Intelligence | 54.5 (13.5) | 63.9 (8.6) | -3.04 | .004 |
| Child Behavior Checklist | | | | |
| Internalizing Symptoms | 59.6 (9.0) | 47.0 (9.8) | 5.02 | <.001 |
| Anxious/Depressed | 53.2 (5.0) | 60.1 (9.2) | 3.54[a] | .001 |
| Withdrawn/Depressed | 60.9 (8.6) | 53.6 (4.2) | 4.11[a] | <.001 |
| Somatic Complaints | 56.4 (7.1) | 52.3 (5.8) | 2.30 | .025 |
| Externalizing Symptoms | 52.1 (10.0) | 43.2 (7.9) | 3.69 | .001 |
| Rule-Breaking Behavior | 54.4 (5.1) | 51.4 (2.2) | 2.74[a] | .008 |
| Aggressive Behavior | 56.0 (6.2) | 51.2 (2.6) | 3.83[a] | <.001 |
| Social Problems | 61.2 (7.8) | 51.5 (3.6) | 6.16[a] | <.001 |
| Thought Problems | 65.0 (7.3) | 51.5 (3.3) | 9.16[a] | <.001 |
| Attention Problems | 63.3 (9.3) | 52.1 (4.1) | 5.98[a] | <.001 |
| Clinical Scales | | | | |
| Affective Problems | 59.1 (7.6) | 53.0 (5.0) | 3.61[a] | .001 |
| Anxiety Problems | 62.4 (8.9) | 53.1 (4.4) | 5.05[a] | <.001 |
| AD/H Problems | 61.2 (7.8) | 51.6 (3.5) | 6.09[a] | <.001 |
| Oppositional Defiance | 55.4 (5.8) | 51.7 (3.4) | 2.97 | .005 |
| Conduct Problems | 55.5 (6.6) | 51.3 (2.8) | 3.20[a] | .003 |
| Total Problems | 59.5 (8.7) | 42.1 (10.2) | 6.89 | <.001 |
| BRIEF | | | | |
| Behavioral Regulation | 64.9 (10.6) | 45.0 (8.5) | 7.67 | <.001 |
| Inhibit | 61.9 (13.0) | 44.9 (6.4) | 6.32[a] | <.001 |
| Shift | 66.1 (9.4) | 45.8 (9.6) | 7.94 | <.001 |
| Emotional Control | 61.5 (12.2) | 46.1 (8.6) | 5.38 | <.001 |
| Metacognition | 63.3 (9.6) | 46.9 (10.8) | 6.29 | <.001 |
| Initiate | 62.7 (9.9) | 46.0 (9.2) | 6.55 | <.001 |
| Working Memory | 64.1 (11.6) | 47.8 (11.3) | 5.29 | <.001 |
| Plan/Organize | 61.2 (10.1) | 47.6 (10.4) | 4.97 | <.001 |
| Organization of Materials | 59.8 (10.2) | 49.9 (12.0) | 3.33 | .002 |
| Monitor | 63.3 (9.6) | 44.9 (10.6) | 6.79 | <.001 |
| Global Executive Composite | 65.6 (9.5) | 45.8 (10.4) | 7.42 | <.001 |
| CPRS-R | | | | |
| DSM Inattention | 67.4 (11.9) | 48.6 (9.2) | 6.52 | <.001 |
| DSM Hyperactivity/Impulsivity | 68.2 (14.7) | 48.8 (8.5) | 6.15[a] | <.001 |
| SCAS | | | | |
| Panic/Agoraphobia | 1.7 (2.9) | 0.3 (0.5) | 2.69[a] | .011 |
| Separation | 3.2 (4.0) | 0.8 (1.5) | 2.99[a] | .005 |
| Physical Injury | 2.9 (2.4) | 1.3 (1.9) | 2.71 | .009 |
| Social Phobia | 4.3 (2.6) | 2.6 (2.0) | 2.72 | .009 |
| Obsessive-Compulsive | 2.3 (3.0) | 0.1 (0.4) | 3.99[a] | <.001 |
| Generalized Anxiety | 3.5 (2.9) | 1.2 (1.1) | 3.91[a] | <.001 |
| Total Anxiety | 18.0 (14.0) | 6.4 (5.4) | 4.17[a] | <.001 |

*Note.* Means (and SDs) are T-scores, with the exception of the SCAS, which uses raw scores. [a] Levene's Test of Equality of Variance indicated that equal variances should not be assumed; therefore, adjusted df values were used in calculations.

Table 2

*Disorder-Specific Symptomatology for ASD Participants in the EFT*

| RBS-R | Number Endorsed | Level of Interference |
|---|---|---|
| Stereotyped Behavior | 3.0 (2.1) | 4.8 (3.9) |
| Self-Injurious Behavior | 1.3 (1.6) | 1.5 (1.9) |
| Compulsive Behavior | 1.9 (1.4) | 2.4 (1.8) |
| Ritualistic Behavior | 2.6 (2.0) | 4.7 (4.4) |
| Sameness Behavior | 3.2 (2.5) | 4.7 (4.2) |
| Restricted Behavior | 1.5 (1.2) | 2.7 (2.6) |
| SRS | T-Score | |
| Social Awareness | 69.9 (12.5) | |
| Social Cognition | 69.8 (12.6) | |
| Social Communication | 73.9 (10.8) | |
| Social Motivation | 74.2 (13.5) | |
| Autistic Mannerisms | 77.2 (13.5) | |
| Total Autistic Features | 78.3 (12.3) | |
| DSM-Oriented Questionnaire | Level of Interference | |
| Home | 3.6 (2.0) | |
| School | 6.1 (1.7) | |
| Social | 7.1 (1.7) | |

*Note.* Means (and SDs) are presented as raw scores on the RBS-R and DSM-Oriented Questionnaire and T-scores on the SRS. Level of interference on the RBS-R is presented on a 0-4 scale, while level of interference on the DSM-Oriented Questionnaire is on a 0-10 scale.

Table 3

*Disorder-Specific Symptomatology for TD Participants in the EFT*

| PTQ | Number Endorsed | Frequency | Intensity |
|---|---|---|---|
| Motor Tics | 3.8 (1.5) | 10.0 (7.1) | 13.8 (12.1) |
| Vocal Tics | 1.2 (1.7) | 3.7 (5.5) | 4.4 (7.0) |
| Total Tics | 5.1 (2.4) | 13.7 (9.2) | 18.2 (14.4) |
| DSM-Oriented Questionnaire | Level of Interference | | |
| Home | 4.5 (2.4) | | |
| School | 5.3 (2.6) | | |
| Social | 4.9 (2.9) | | |

*Note.* Means (and SDs) are presented as raw scores. Scales for frequency (1-4 per tic) and intensity (0-8 per tic) were cumulative. Level of interference is on a 0-10 scale.

**Performance Measures**

Performance measures for the two groups are presented in Table 4. On average, participants made 52 (*SD*: 28) errors, and the number of errors did not vary as a function of group, $t(54)<1$. A 2 (group) x 2 (trial type) repeated-measures analysis of variance (ANOVA) indicated that participants had faster overall reaction times (RTs) when they made erroneous, rather than correct, responses, $F(1,54)=112.84$, $p<.001$, $\eta_p^2 = .676$. However, groups did not differ on RT, $F(1,54)<1$, and there was no interaction between group and trial type on RT, $F(1,54)<1$. A 5 (age) x 2 (trial type) repeated-measures ANOVA (see the *ERP measures' Effects of age* section for description of ages) found that neither overall RT, $F(4,51)=2.06$, $p=.01$, nor the difference in RT between correct and error trials, $F(4,51)<1$, varied as a function of age.

To assess the role of conflict (i.e., high- vs. low-conflict), RTs and accuracy were independently submitted to 2 (group) x 2 (level of conflict) repeated measures ANOVAs. RT analyses yielded a main effect of level of conflict, $F(1,54)=135.83$, $p<.001$, such that participants had longer RTs on incongruent, compared to congruent, trials. There was neither an effect of group, $F(1,54)<1$, nor an interaction of group and level of conflict, $F(1,54)<1$. Regarding accuracy, there was a main effect of level of conflict, $F(1,54)=139.14$, $p<.001$, such that participants made more errors on incongruent than congruent trials. Accuracy did not vary as a function of group, $F(1,54)=2.56$, $p=.115$, or as an interaction of group by level of conflict, $F(1,54)=1.16$, $p=.287$.

Post-error performance (RT and accuracy) was compared to overall performance in a 2 (group) x 2 (trial type) repeated-measures ANOVA. Post-error RTs did not differ

from overall RTs, $F(1,54)=1.97$, $p=.17$. There was neither a main effect of group, $F(1,54)<1$, nor a group by trial type interaction, $F(1,54)<1$. A 5 (age) x 2 (trial type) repeated-measures ANOVA similarly revealed no effect of age, $F(4,51)=1.45$, $p=.230$, nor an age by trial type interaction, $F(4,51)<1$. Accuracy was worse on trials following errors, $F(1,54)=8.40$, $p=.005$, $\eta_p^2=.135$. There was neither a main effect of group on accuracy, $F(1,54)=1.06$, $p=.309$, nor a group by trial type interaction, $F(1,54)<1$. Post-trial accuracy also did not vary as a function of age, $F(4,51)=2.14$, $p=.089$, or age by trial type interaction, $F(4,51)<1$.

Table 4

*Performance Data across Groups in the EFT*

| | RB | TDC |
|---|---|---|
| Reaction Time (ms) | | |
| Overall | 234.2 (102.3) | 218.1 (52.4) |
| Error | 146.9 (44.0) | 146.9 (44.0) |
| Correct | 251.9 (114.9) | 233.5 (54.8) |
| Congruent Trials | 216.1 (11.0) | 200.5 (53.1) |
| Incongruent Trials | 256.6 (116.8) | 241.9 (58.7) |
| Accuracy | | |
| Number of Errors | 54.7 (29.1) | 48.4 (26.0) |
| Overall (%) | 79.6 (10.1) | 82.5 (9.6) |
| Congruent Trials (%) | 88.3 (10.1) | 91.0 (9.0) |
| Incongruent Trials (%) | 68.0 (15.1) | 74.1 (11.6) |
| Post-Error Behavior | | |
| Post-Error RT (ms) | 222.4 (117.5) | 207.3 (60.9) |
| Post-Error Accuracy (%) | 75.0 (13.8) | 78.8 (18.6) |

*Note.* Means (and SDs) are presented.

**ERP Measures**

Figure 1 presents topographic maps of the average voltages across the scalp from all participants during error trials. Consistent with literature, the head plots confirmed that five fronto-central electrodes (Fz, FC1, FCz, FC2, Cz) have the greatest error-related negativity, and five slightly more posterior electrodes (Cz, CP1, CPz, CP2, Pz) have the greatest error-related positivity. Based on the sites of maximal electrical activity for unadjusted data, subsequent single-electrode analysis, using the Woody Filter technique, was conducted at FCz for error-related negativity and CPz for error-related positivity.

Figures 1a and 2a present grand average unadjusted and Woody filtered ERN data, respectively. Both analysis procedures indicate that when an error was committed, there was a sharp, negative deflection that peaked, on average, at 43 ms post-response. As is detailed in *Effects of Group* below, results of both analysis procedures yielded main effects of trial type, such that there was significantly more negativity in the 0 to 100 ms time window on error trials than on correct-response trials.

Figures 1c and 2b present grand average unadjusted and Woody filtered Pe data, respectively. While both analysis procedures confirmed error-related positivity in the expected time window, unadjusted data yielded maximal positivity at 133 ms post-response, and Woody filtered data yielded maximal positivity at 158 ms post-response. As with ERN data, analyses using both procedures yielded main effects of trial type, such that there was significantly more positivity in the 100-300 ms time window on error trials than on correct-response trials.

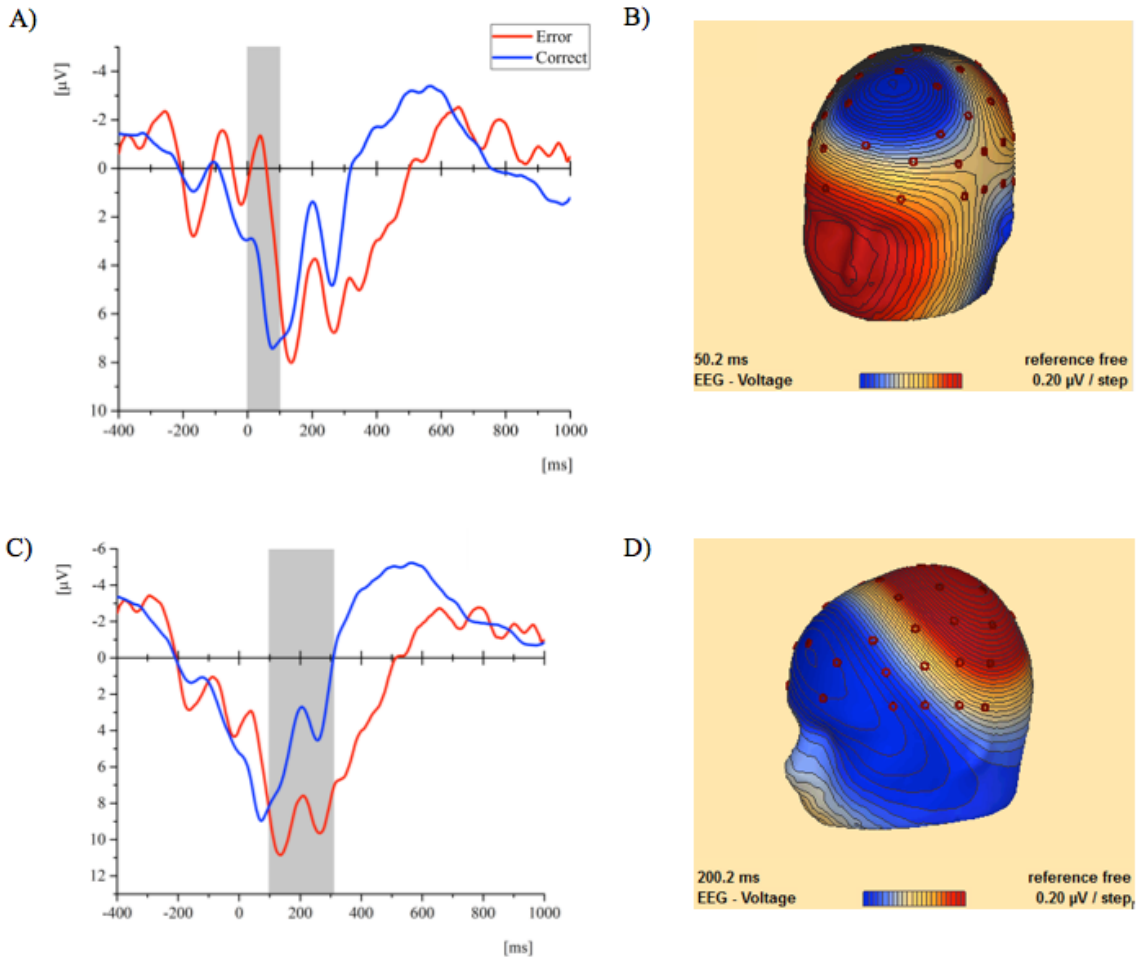


Figure 1

*Grand Average Waveforms and Topographic Maps for the EFT*

Grand average ERPs in the (a) ERN ROI and (c) Pe ROI, as well as respective topographic maps of scalp voltage at (b) ~50 ms and (d) ~200 ms after an incorrect button press.

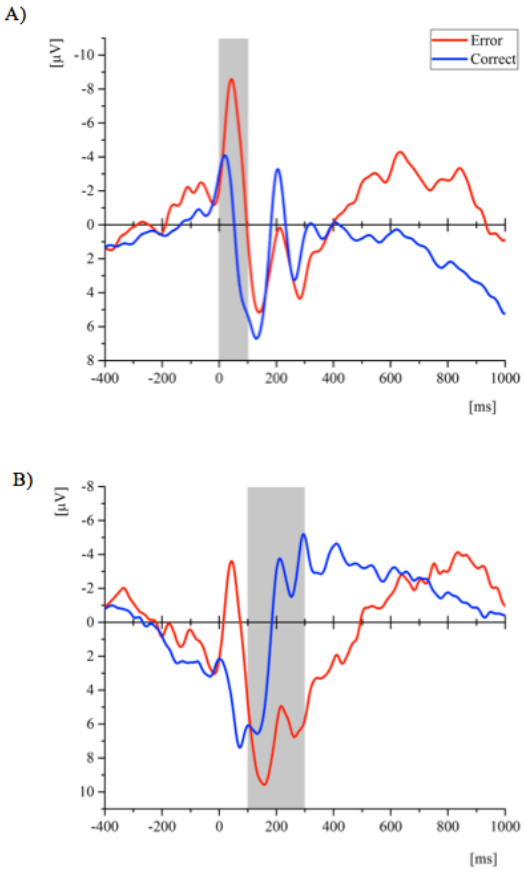


Figure 2

*Woody Filtered Grand Average Waveforms for the EFT*

Grand average ERPs at (a) FCz and (b) CPz after Woody filtering.

***Effects of Group.*** To evaluate indicators of interference control problems in repetitive behaviors (Aim 1), error-related brain activity components were analyzed by group. Primary (unadjusted) analyses and secondary, latency-corrected (Woody filtered) single-electrode analyses are presented separately by component below. ERP waveforms are presented by group in Figure 3 for unadjusted data and Figure 4 for Woody filtered data. To allow for visual comparison of outcomes produced through unadjusted and Woody filtering procedures, difference waves were created for each procedure by subtracting the correct from the incorrect ERP waveform and are presented in Figure 5. These waveforms include the difference in negativity (i.e., dERN) and positivity (i.e., dPe) between error and correct trials for the RB and TDC groups.

*Unadjusted ERN.* A 2 (group) x 2 (trial type) repeated-measures ANOVA confirmed that there was significantly more negativity on error trials than on correct-response trials, $F(1,54)=18.27$, $p<.001$, $\eta_p^2=.253$. However, the hypothesis that ERN mean amplitude would vary between RB and TDC groups was disconfirmed, as there was neither an effect of group, $F(1,54)<1$, nor a group by trial type interaction, $F(1,54)<1$.

*Woody filtered ERN.* Consistent with unadjusted data, a 2 (group) by 2 (trial type) repeated-measures ANOVA confirmed that there was significantly more negativity on error trials than on correct-response trials, $F(1,54)=15.08$, $p<.001$, $\eta_p^2=.218$, but neither an effect of group, $F(1,54)<1$, nor a group by trial type interaction, $F(1,54)<1$.

*Unadjusted Pe.* A 2 (group) x 2 (trial type) repeated-measures ANOVA confirmed that the Pe component was significantly more positive on error trials than on correct-response trials, $F(1,54)=17.25$, $p<.001$, $\eta_p^2=.242$. While there was no main effect

of group, $F(1,54)<1$, there was a significant group by trial type interaction, $F(1,54)=4.35$, $p=.042$, $\eta_p^2=.075$, such that the difference in positivity between error and correct trials (i.e., dPe) was significantly smaller in the RB group than the TDC group.

*Woody filtered Pe.* A 2 (group) x 2 (trial type) repeated-measures ANOVA corroborated the aforementioned main effect of trial type, $F(1,54)=10.22$, $p=.002$, $\eta_p^2=.159$. Consistent with the unadjusted data, amplitude did not vary by group, $F(1,54)<1$. However, the group by trial type interaction did not reach significance after Woody filtering, $F(1,54)=2.95$, $p=.092$.

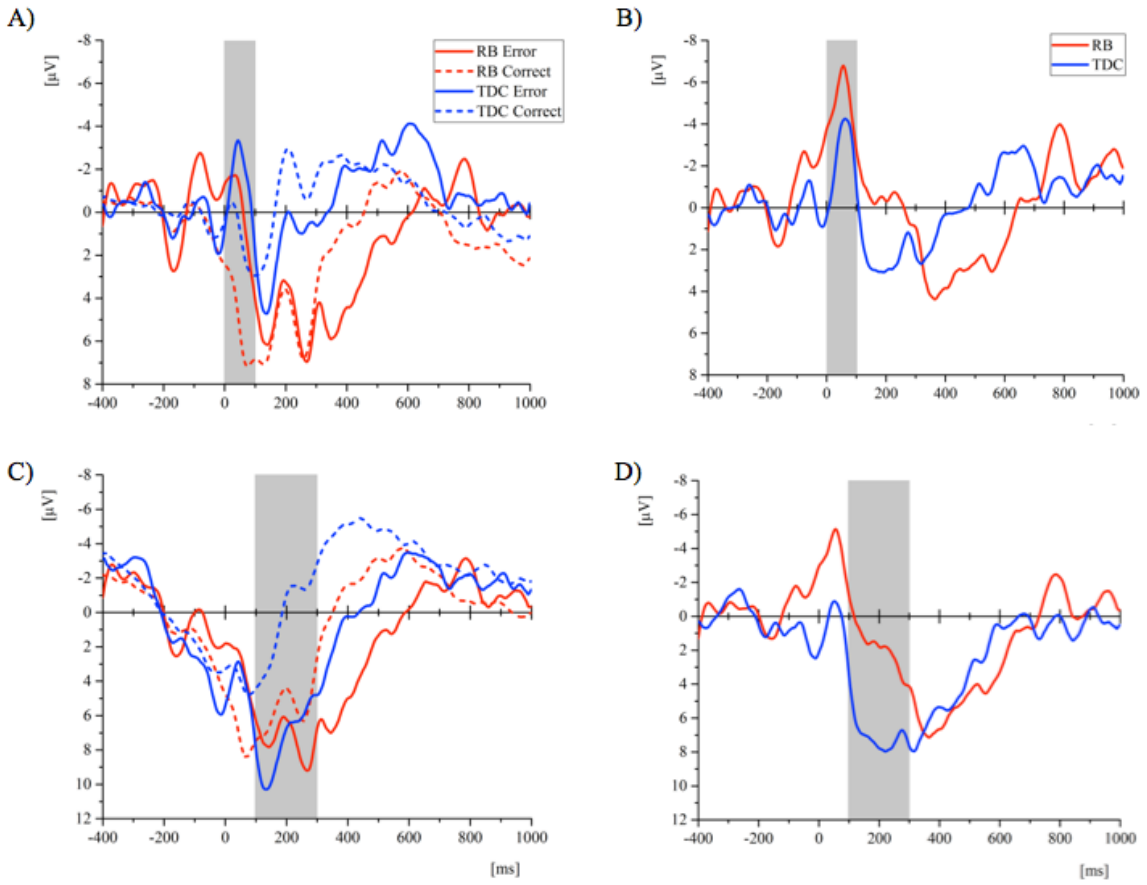


Figure 3

*ERP Waveforms by Group for the EFT*

(a) Error, correct, and (b) difference waveforms in the ERN ROI by group. (c) Error, correct, and (d) difference waveforms in the Pe ROI by group.

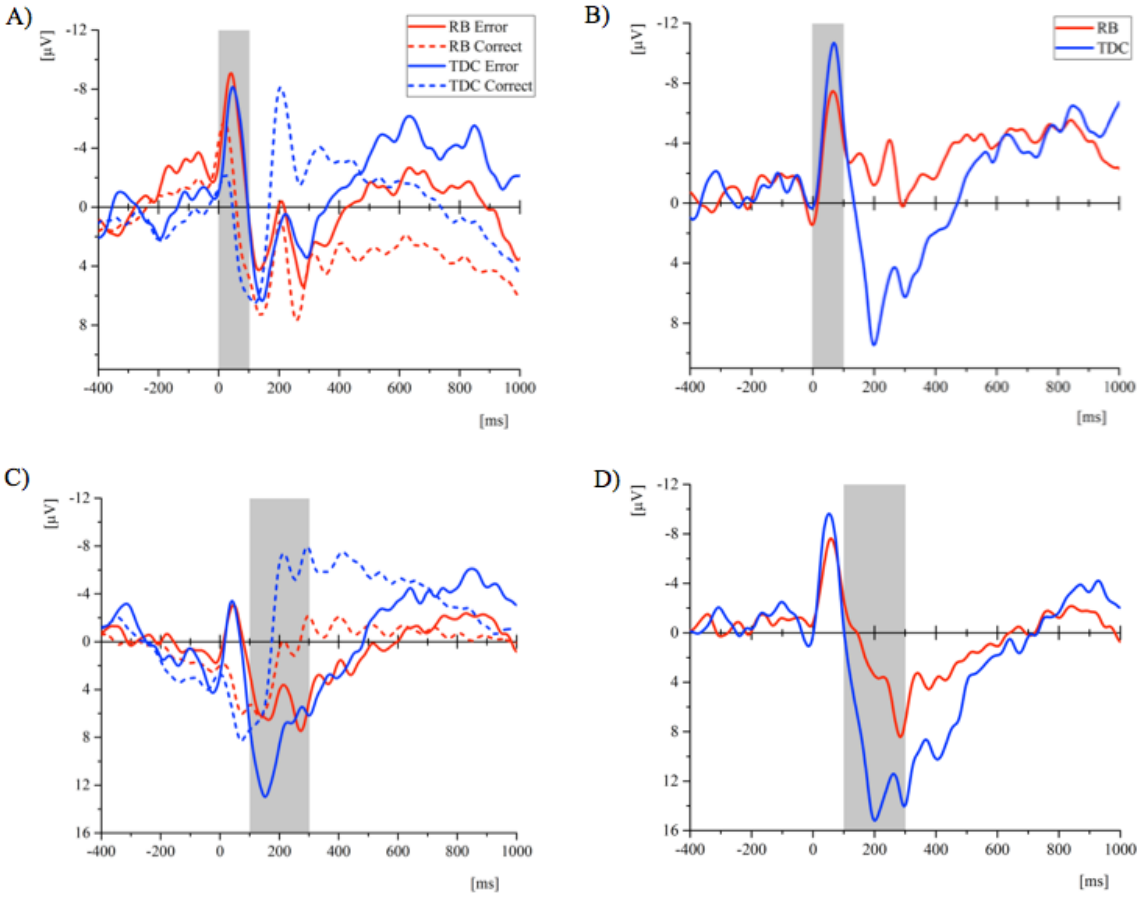


Figure 4

*Woody filtered ERP Waveforms by Group for the EFT*

(a) Error, correct, and (b) difference waveforms at FCz by group. (c) Error, correct, and (d) difference waveforms at CPz by group.

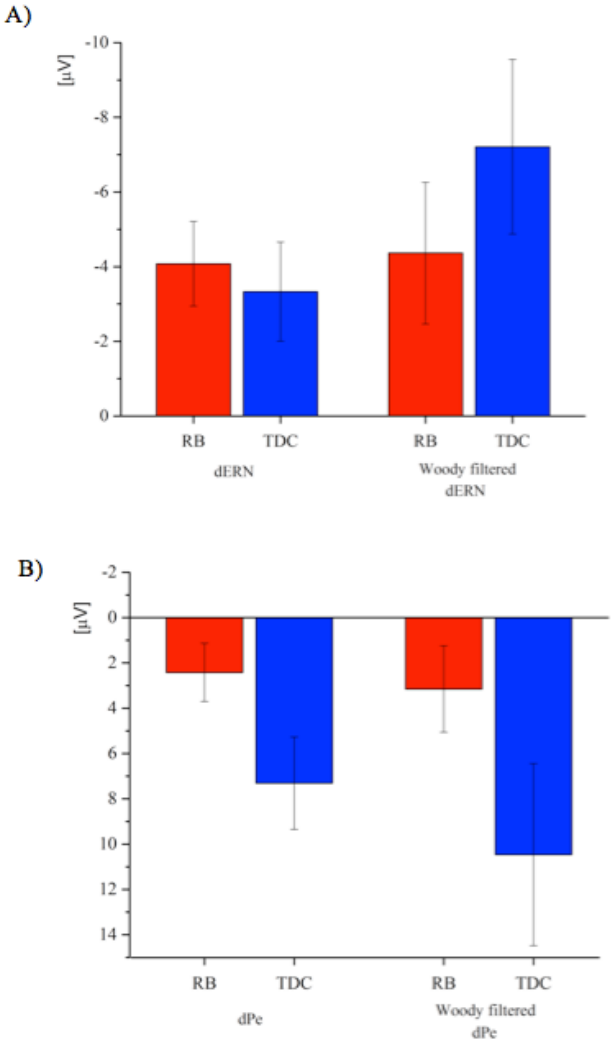


Figure 5

*Mean Amplitudes by Group and Filtering Technique for the EFT*

(a) dERN and (b) dPe mean amplitudes by filtering technique and group. dERN and dPe mean amplitudes were measured at their respective ROIs; woody filtered dERN and dPe mean amplitudes were measured at FCz and CPz, respectively.

***Effects of Age.*** To explore the role of age on the magnitude of error-related brain activity, ERP data were first analyzed continuously. Age and ERP component (ERN, CRN, dERN, Pe, Pc, dPe) amplitude were not significant correlated in either unadjusted or Woody filtered data. The potential relationship was further explored by examining ERP amplitudes across five ages bins: 8-9 year-olds (N=3), 10-11 year-olds (N=12), 12-13 year-olds (N=21), 14-15 year-olds (N=11), and 16-17 year-olds (N=9). ERP waveforms are presented by age in Figure 6.

*Unadjusted ERN.* A 5 (age) by 2 (trial type) repeated-measures ANOVA yielded a main effect of trial type, $F(1,51)=26.83$, $p<.001$, $\eta_p^2=.345$, such that the ERN was significantly larger than the CRN. Further, the difference between the ERN and CRN varied as a function of age, $F(4,51)=3.72$, $p=.010$, $\eta_p^2=.226$. Follow-up paired-samples *t*-tests confirmed that the ERN is reliably more negative than the CRN in 10-11 year-olds, $t(11)=-3.14$, $p=.009$, and 16-17 year-olds, $t(8)=-2.69$, $p=.027$. The ERN was not reliably larger than the CRN in the 8-9 year-olds, $t(2)=-2.71$, $p=.113$, 12-13 year-olds, $t(20)=-1.82$, $p=.083$, and the 14-15 year-olds, $t(10)=0.003$, $p=.998$. There was no effect of age, $F(4,51)=1.72$, $p=.160$.

*Woody filtered ERN.* Following application of the Woody filter procedure, a 5 (age) by 2 (trial type) repeated-measures ANOVA indicated a maintained main effect of trial type, $F(1,51)=10.87$, $p=.002$, $\eta_p^2=.176$, and a marginally nonsignificant effect of age, $F(4,51)=2.52$, $p=.053$. The age by trial type interaction found in the unadjusted ERN data did not reach significance, $F(4,51)<1$. Although effects did not reach significance, paired-samples *t*-tests were run for an exploratory comparison to the results of the unadjusted

data. Results indicated that the ERN was reliably more negative than the CRN in only the 16-17 year-olds, $t(8)=-6.78$, $p<.001$. This magnitude differential did not reach significance in 8-9 year-olds, $t(2)=-0.44$, $p=.703$, 10-11 year-olds, $t(11)=-1.68$, $p=.121$, 12-13 year-olds, $t(20)=-1.36$, $p=.191$, and 14-15 year-olds, $t(10)=-1.78$, $p=.106$.

*Unadjusted Pe.* Consistent with the ERN data, there was a main effect of trial type, $F(1,51)=6.16$, $p=.016$, $\eta_p^2=.108$, such that the Pe was significantly larger than the Pc. However, in contrast to the unadjusted ERN data, the magnitudes of the components did not differ as a function of age, as a 5 (age) by 2 (trial type) repeated-measures ANOVA yielded neither an effect of group, $F(4,51)=1.86$, $p=.132$, nor a group by trial type interaction, $F(4,51)<1$.

*Woody filtered Pe.* Consistent with analyses from unadjusted Pe data, a 5 (age) by 2 (trial type) repeated-measures ANOVA indicated a maintained effect of trial type, $F(1,51)=6.16$, $p=.016$, $\eta_p^2=.108$, but neither an effect of group, nor a group by trial type interaction, $F$s$(4,51)<1$.

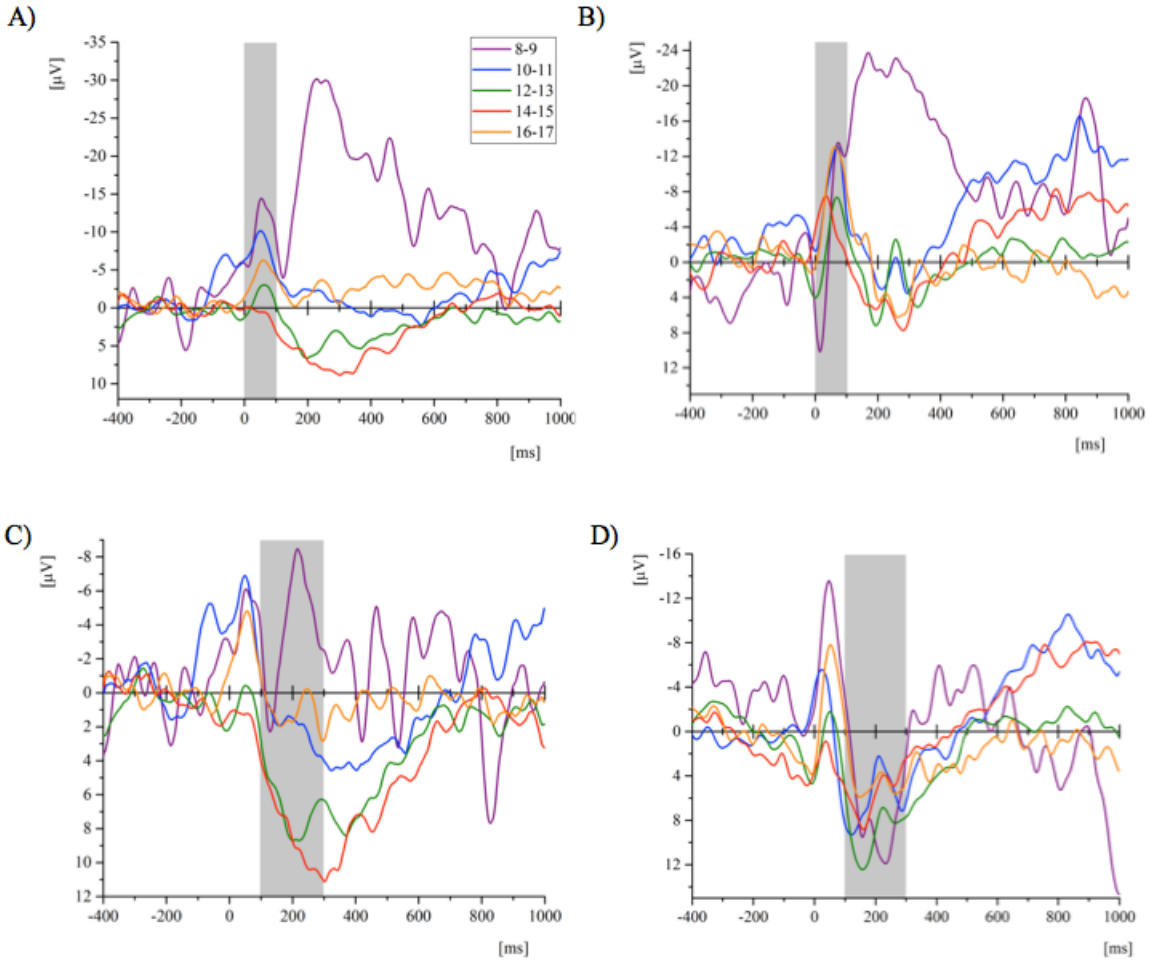


Figure 6

*ERP Difference Waveforms by Age and Filtering Technique for the EFT*

dERN waveforms by age using (a) standard analysis in the ERN ROI and (b) the Woody Filter technique at FCz. dPe waveforms by age using (c) standard analysis in the Pe ROI and (d) the Woody Filter technique at CPz.

## Task 2: Motor Inhibition

### Participants

Of the 76 individuals who attended the study, 74 completed the SST. As noted above, one individual discontinued after fainting during EEG electrode application. A second individual experienced sensory sensitivities during the EFT and elected to discontinue prior to the SST. Of the 74 individuals who completed the EEG task, the data from 17 subjects (23.0%) were excluded from analysis: 8 for excessive movement yielding too few usable trials, 7 for too many (>20%) omissions on go-trials, and 2 for too few (<30%) successful stops. Thus, the final sample consisted of 57 participants, 44 (77.2%) of whose data were also included in EFT analyses. Of the 57 useable participants, group composition was 32 RB (27 males) and 25 TDC (20 males) participants. Chi-square analysis indicated that the groups did not differ significantly in terms of gender, $\chi^2(1)=0.19$, $p=.67$. The mean age for the RB group was 13.2 (*SD*: 2.1), and the mean age of the TDC group was 13.7 (*SD*: 2.3) with pubertal development scores of 12.0 (*SD*: 4.1) and 12.4 (*SD*: 3.9), respectively. One-way ANOVAs with 2 between-group levels indicated that neither age, nor pubertal development, differed as a function of group status, $F(1,55)<1$.

### Psychological Profiles of Participants

Table 5 presents the psychological characteristics of the sample, including *t*-statistics and *p*-values for all between-group comparisons. On the Raven's Progressive Matrices, the RB group demonstrated comparable nonverbal intelligence to the TDC

group, $t(52.039^{4})=1.93$, $p=.004$. Parent-report questionnaires indicated that the RB group had significantly higher levels of psychopathology across all measured internalizing and externalizing domains (CBCL), behavior regulation and metacognitive executive functions (BRIEF), inattention and hyperactivity/impulsivity (CPRS-R), and anxiety (SCAS).

Disorder-specific symptomatology for individuals in the RB group is reported in Tables 6 and 7. Participants with ASD met Criteria A-C. For individuals with ASD, symptoms were, on average, first noticed at 2.7 (*SD*: 1.3) years old. At present, they endorsed an average of 12.6 (*SD*: 8.8) repetitive behaviors, which most often fell into the categories of stereotyped, ritualistic, and sameness behaviors. These were accompanied, on average, by a *severe* level of social difficulties on the SRS, although *mild to moderate* difficulties were reported across all categories: social awareness, social cognition, social communication, social motivation, and autistic mannerisms.

Individuals with TD also qualified for the maintenance of their diagnosis per parent-reported questionnaires. Symptom onset was, on average, at 5.2 (*SD*: 3.8) years old, indicating over a year of interference and their neurodevelopmental nature. Frequency and level of interference by tics fell in the *moderate* range overall. Individuals with TD endorsed an average of 5.0 (*SD*: 2.6) tics, more of which were motor than vocal.

Across both RBs, parent-reported interference indicated moderate levels of disorder-specific symptom interference across settings, further supporting that the participants continue to meet diagnostic criteria for their respective disorders. Individuals

[4] Levene's Test of Equality of Variance indicated that equal variances should not be assumed.

with ASD did not significantly differ from those with TD in symptom interference across home, $t(30)=-0.36$, $p=.724$ or school, $t(30)=0.45$, $p=.658$. However, individuals with ASD did experience significantly more symptom interference in social settings, $t(30)=2.38$, $p=.024$.

The psychological characteristics of included and excluded participants were again examined to determine if the subset included in analyses was representative of the larger sample. Overall, data from the RB group revealed a similar pattern to in the EFT, such that those included were slightly less severe in disorder-specific symptomatology than those excluded. Specifically, relative to their excluded counterparts, those included with TD endorsed fewer vocal tics, $t(8)=-2.899$, $p=.020$, with associated lower frequency, $t(8)=-3.841$, $p=.005$, and intensity, $t(8)=-6.375$, $p<.001$, of these tics. While included and excluded individuals with ASD endorsed a comparable number of repetitive behaviors, those included reported significantly less interference caused by their repetitive behaviors, $t(31)=-2.044$, $p=.050$. Included and excluded RB participants did not differ on index or subscale measurements on the CBCL, BRIEF, CPRS-R, or SCAS.

Whereas psychological characters of included and excluded TDC participants were largely comparable in the EFT, in the Stop-Signal Task, the included TDC participants had higher levels of executive function-related psychopathology in several areas than the excluded participants. Specifically, included participants had higher levels of inattention, $t(29.971^{5})=2.437$, $p=.021$, ADHD symptoms, $t(25.548)=2.668$, $p=.013$, on the CBCL, as well as more difficulties with initiation, $t(30)=2.836$, $p=.008$, and working

[5] Levene's Test of Equality of Variance indicated that equal variances should not be assumed.

memory, $t(26.221^{5})=3.320$, $p=.003$, on the BRIEF. Included and excluded TDC participants did not differ on the CPRS-R or SCAS.

Table 5

*Psychological Profiles of Participants by Group in the Stop-Signal Task*

| | RB | TDC | *t*-statistic | *p*-value |
|---|---|---|---|---|
| Raven's Progressive Matrices | | | | |
| Nonverbal intelligence | 57.3 (13.9) | 63.0 (8.4) | -1.93[a] | .059 |
| Child Behavior Checklist | | | | |
| Internalizing Symptoms | 60.1 (9.3) | 47.0 (9.6) | 5.21 | <.001 |
| Anxious/Depressed | 61.6 (10.0) | 53.1 (5.4) | 4.14[a] | <.001 |
| Withdrawn/Depressed | 60.4 (9.1) | 53.3 (3.5) | 4.07[a] | <.001 |
| Somatic Complaints | 56.2 (5.9) | 52.2 (5.3) | 2.63 | .011 |
| Externalizing Symptoms | 51.9 (9.6) | 42.9 (6.9) | 3.95 | <.001 |
| Rule-Breaking Behavior | 54.1 (4.9) | 51.0 (1.4) | 3.36[a] | .002 |
| Aggressive Behavior | 55.6 (6.1) | 50.8 (1.8) | 4.19[a] | <.001 |
| Social Problems | 60.7 (7.7) | 51.2 (2.1) | 6.61[a] | <.001 |
| Thought Problems | 65.4 (7.9) | 51.5 (3.3) | 9.04[a] | <.001 |
| Attention Problems | 62.3 (6.7) | 52.8 (4.5) | 6.09 | <.001 |
| Clinical Scales | | | | |
| Affective Problems | 59.6 (8.3) | 53.3 (4.8) | 3.61[a] | .001 |
| Anxiety Problems | 63.8 (8.4) | 53.3 (5.1) | 5.82[a] | <.001 |
| AD/H Problems | 61.1 (7.2) | 52.2 (3.9) | 5.94[a] | <.001 |
| Oppositional Defiance | 54.7 (5.6) | 51.5 (3.2) | 2.69[a] | .010 |
| Conduct Problems | 54.8 (6.1) | 50.7 (1.5) | 3.70[a] | .001 |
| Total Problems | 59.7 (8.3) | 43.0 (9.1) | 7.18 | <.001 |
| BRIEF | | | | |
| Behavioral Regulation | 64.6 (10.1) | 46.1 (8.3) | 7.43 | <.001 |
| Inhibit | 61.5 (12.0) | 46.2 (6.2) | 6.21[a] | <.001 |
| Shift | 66.3 (10.5) | 47.2 (8.9) | 7.25 | <.001 |
| Emotional Control | 61.0 (12.2) | 46.5 (8.5) | 5.30[a] | <.001 |
| Metacognition | 63.9 (9.1) | 48.4 (9.7) | 6.15 | <.001 |
| Initiate | 63.0 (9.1) | 48.0 (8.4) | 6.41 | <.001 |
| Working Memory | 64.1 (11.0) | 49.7 (11.3) | 4.83 | <.001 |
| Plan/Organize | 61.8 (9.9) | 48.7 (9.3) | 5.06 | <.001 |
| Organization of Materials | 59.7 (10.0) | 50.9 (11.6) | 3.07 | .003 |
| Monitor | 62.5 (10.1) | 45.4 (8.4) | 6.83 | <.001 |
| Global Executive Composite | 65.4 (9.0) | 48.4 (9.7) | 7.31 | <.001 |
| Conners-3 | | | | |
| DSM Inattention | 67.4 (11.3) | 59.6 (14.0) | 6.13 | <.001 |
| DSM Hyperactivity/Impulsivity | 69.1 (14.1) | 40.5 (10.1) | 5.56 | <.001 |
| SCAS | | | | |
| Panic/Agoraphobia | 1.5 (2.2) | 0.2 (0.5) | 3.22[a] | .003 |
| Separation | 3.1 (3.7) | 0.7 (1.1) | 3.42[a] | .002 |
| Physical Injury | 2.7 (2.5) | 1.4 (1.6) | 2.42 | .019 |
| Social Phobia | 4.6 (2.7) | 2.8 (2.2) | 2.67 | .010 |
| Obsessive-Compulsive | 2.5 (3.0) | 0.2 (0.5) | 4.13[a] | <.001 |
| Generalized Anxiety | 3.8 (3.0) | 1.4 (1.4) | 3.95[a] | <.001 |
| Total Anxiety | 17.7 (13.5) | 6.6 (5.2) | 4.24[a] | <.001 |

*Note.* Means (and SDs) are T-scores, with the exception of the SCAS, which uses raw scores. [a] Levene's Test of Equality of Variance indicated that equal variances should not be assumed; therefore, adjusted df values were used in calculations.

Table 6

*Disorder-Specific Symptomatology for ASD Participants in the Stop-Signal Task*

| RBS-R | Number Endorsed | Level of Interference |
|---|---|---|
| Stereotyped Behavior | 3.8 (2.6) | 2.5 (2.0) |
| Self-Injurious Behavior | 1.8 (3.0) | 1.1 (1.6) |
| Compulsive Behavior | 2.5 (2.5) | 2.0 (1.9) |
| Ritualistic Behavior | 4.2 (3.5) | 2.5 (1.9) |
| Sameness Behavior | 5.3 (4.7) | 3.7 (2.7) |
| Restricted Behavior | 3.0 (2.8) | 1.8 (1.4) |
| SRS | T-Score | |
| Social Awareness | 68.2 (13.1) | |
| Social Cognition | 69.3 (12.8) | |
| Social Communication | 70.9 (11.0) | |
| Social Motivation | 72.1 (14.9) | |
| Autistic Mannerisms | 74.1 (17.1) | |
| Total Autistic Features | 76.1 (13.5) | |
| DSM-Oriented Questionnaire | Level of Interference | |
| Home | 3.9 (2.4) | |
| School | 5.8 (1.8) | |
| Social | 7.0 (1.9) | |

*Note.* Means (and SDs) are presented as raw scores on the RBS-R and DSM-Oriented Questionnaires and T-scores on the SRS. Level of interference on the RBS-R is presented on a 0-4 scale, while level of interference on the DSM-Oriented Questionnaire is on a 0-10 scale.

Table 7

*Disorder-Specific Symptomatology for TD Participants in Stop-Signal Task*

| PTQ | Number Endorsed | Frequency | Intensity |
|---|---|---|---|
| Motor Tics | 4.1 (1.4) | 10.6 (7.3) | 14.6 (12.6) |
| Vocal Tics | 0.9 (1.5) | 2.1 (3.1) | 2.4 (3.5) |
| Total Tics | 5.0 (2.6) | 12.8 (9.4) | 17.0 (14.9) |
| DSM-Oriented Questionnaire | Level of Interference | | |
| Home | 4.3 (2.7) | | |
| School | 5.4 (2.8) | | |
| Social | 4.8 (3.1) | | |

*Note.* Means (and SDs) are presented as raw scores. Scales for frequency (1-4 per tic) and intensity (0-8 per tic) were cumulative. Level of interference on the RBS-R is presented on a 0-4 scale, while level of interference on the DSM-Oriented Questionnaire is on a 0-10 scale.

**Performance Measures**

Table 8 presents performance measures that were used to calculate the SSRT, including the average stop signal delay and the go-trial RT associated with 50% accuracy on stop-trials. Overall, groups showed no difference in stop accuracy, $t(39.594)=1.37$, $p=.178$, indicating that the tracking procedure effectively adjusted stop signal delays to achieve approximately 50% accuracy in both groups. Consistent with the horse-race model, the average length of the stop signal delay following onset of the go-stimulus was significantly shorter for successful trials than unsuccessful trials, $t(56)=-8.30$, $p<.001$. This effect did not vary by group, $F(1,55)=1.68$, $p=.200$, or age, $F(3,53)=1.05$, $p=.377$. Independent-sample *t*-tests revealed no between-group differences in the number of go-trials omitted, $t(55)<1$, in the go-trial RT associated with ~50% accuracy on stop-trials, $t(55)<1$, or in the SSRT, $t(55)=1.07$, $p=.290$. One-way ANOVAs with age as a between-subjects factor similarly indicated that omissions, go-trial RT, and SSRT did not vary as a function of age, $F$s$(3,53)<1$.

Table 8

Performance Data across Groups in Stop-Signal Task

| | RB | TDC |
|---|---|---|
| Stop Accuracy (%) | 51.0 (7.1) | 52.8 (2.3) |
| Stop Signal Delay (ms) | 411.5 (129.8) | 405.6 (157.1) |
| Successful | 392.9 (117.2) | 376.3 (150.2) |
| Unsuccessful | 438.9 (146.3) | 439.1 (167.9) |
| Go RT (ms) | 671.8 (146.6) | 655.9 (175.5) |
| Stop-Signal Reaction Time (ms) | 266.5 (63.6) | 250.4 (46.5) |
| Omits | 9.6 (9.6) | 7.2 (9.3) |

*Note*. Means (and SDs) are presented.

**ERP Measures**

Consistent with literature, visual inspection of the head plots, presented in Figure 7, revealed a lateralized, anterior distribution of the stop-trial N2, such that N2 appeared largest on the right side of the scalp. Based on regions of maximal activation, lateralized groups of electrodes were selected to comprise the right and left ROIs (i.e., right: C4, FC6, C6, CP6, T8; left: C3, FC5, C5, CP5, T7). The ERPs of the respective electrodes were averaged together to quantify each component. Statistical analysis of the apparent laterality effect was conducted through paired-sample *t*-tests, which indicated that while the right ROI had a more negative mean amplitude overall, right and left N2 amplitudes did not differ significantly from each other for either successful, $t(56)=-1.50$, $p=.138$, or unsuccessful, $t(56)=-1.01$ $p=.315$, trials. As the peak amplitude in the grand average waveforms was approximately 185 ms for both SST and USST conditions, the 50 ms time window centered on this latency value (160-210 ms) was used for measurement of N2 mean amplitude for all analyses.

With regard to the P3, visual inspection indicated that the latency and topographic distribution of the P3 effects differed between SSTs and USSTs. Consistent with literature, the no-go P3 to SSTs occurred earlier (i.e., grand average peak amplitude: 280 ms) and with a more fronto-central midline distribution, and the P3 to USSTs occurred later (i.e., grand average peak amplitude: 350 ms) and with a more posterior midline distribution. Frontal-central and centro-parietal midline ROIs were selected based on areas of maximal activation for the SST P3 (i.e., Fz, FC1, FC2, FCz) and USST P3 (i.e., CPz, CP1, CP2, Pz). Consistent with the approach taken to determine the measurement

window for N2, 50 ms time windows surrounding the grand average peak amplitudes were established as measurement windows for the frontal, no-go P3 to SSTs (255-305 ms) and the posterior P3 to USSTs (325-375 ms).

Statistical analyses were conducted to assess effects of ROI. Paired-sample *t*-tests revealed that the P3 amplitude on SSTs was significantly larger in the anterior, compared to the posterior, ROI, $t(56)=2.19$, $p=.033$. P3 amplitude on USSTs, however, did not significantly vary across ROIs, $t(56)=1.18$, $p=.245$.

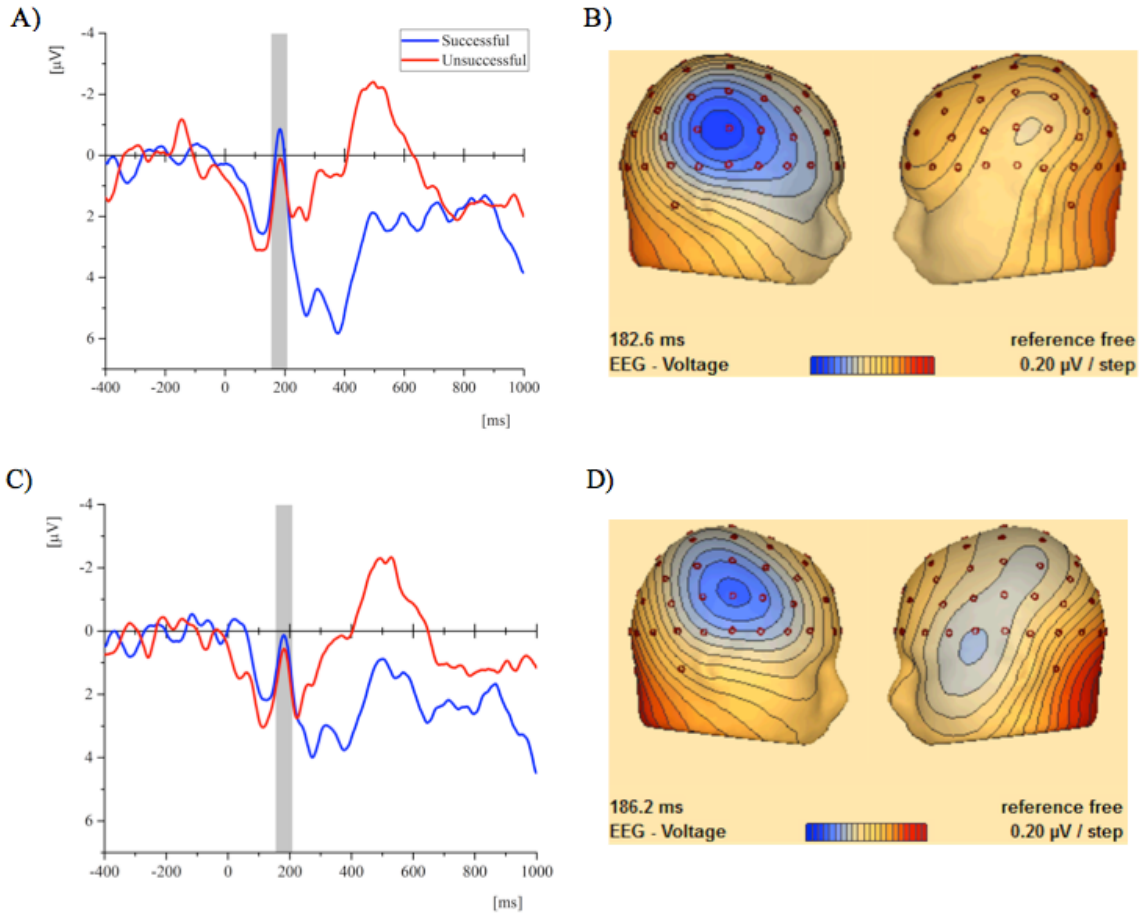


Figure 7

*Grand Average N2 Waveforms and Topographic Maps for the Stop-Signal Task*

Topographic maps of scalp voltage at ~180 ms revealed a lateralized distribution of N2 effects for both (b) successful and (d) unsuccessful stop trials. Accordingly, grand average N2 waveforms for successful and unsuccessful trials are presented in the (a) right and (c) left ROIs.

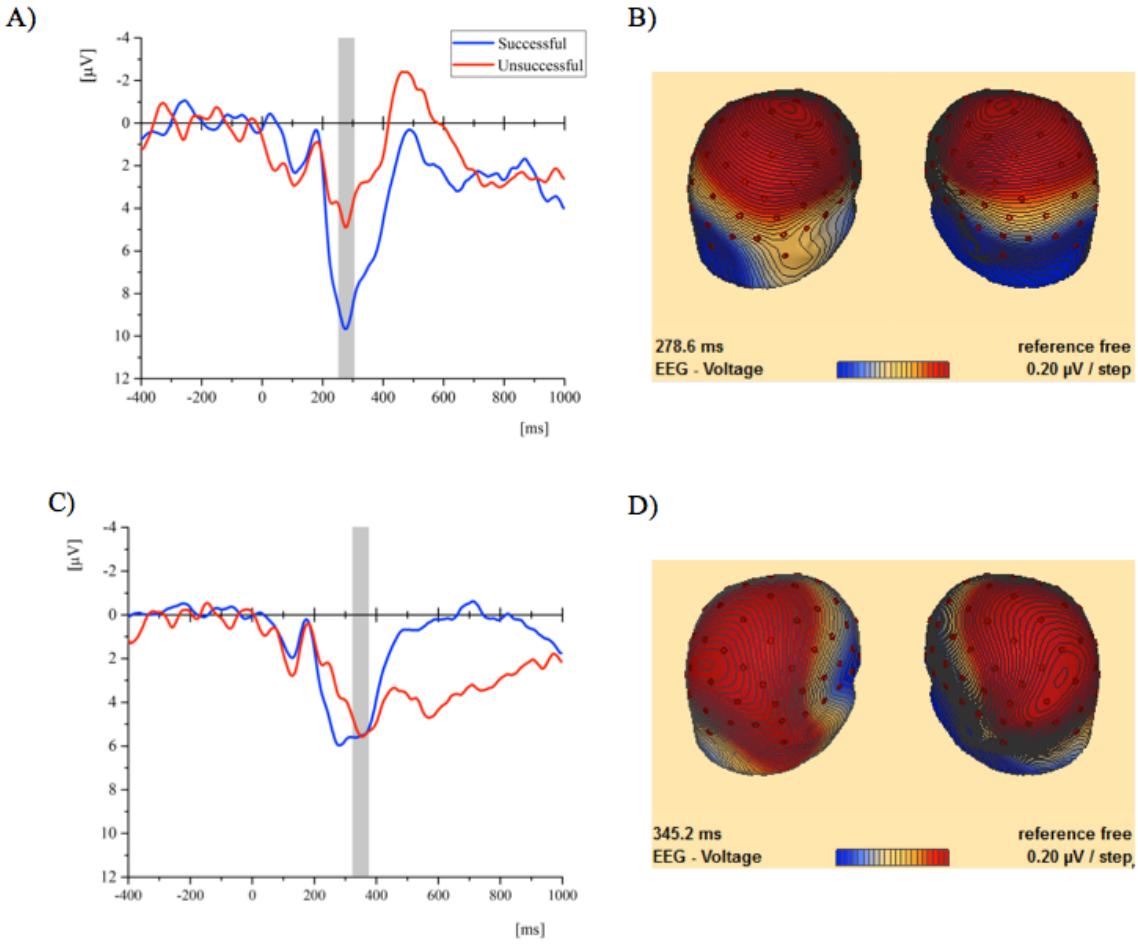


Figure 8

*Grand Average P3 Waveforms and Topographic Maps for the Stop-Signal Task*

Topographic maps of scalp voltage revealed that (b) maximal voltage for SST occurred earlier and with a fronto-central midline scalp distribution, and (d) maximal voltage for the USST occurred later and with a more posterior scalp distribution. Grand average ERPs are presented for SST and USST conditions at the (a) anterior and (c) posterior ROIs.

***Effects of Group.*** To evaluate indicators of conflict monitoring and conflict resolution problems in repetitive behaviors (Aim 2), ERP components associated with successful and unsuccessful response inhibition were analyzed by group. Figure 9 presents ERP waveforms at the N2 ROIs, and Figure 10 presents ERP waveforms at the P3 ROIs.

*N2.* A 2 (trial type) by 2 (laterality) by 2 (group) repeated-measures ANOVA indicated no main effects of trial type, $F(1,55)=1.27$, $p=.264$, laterality, $F(1,55)=1.58$, $p=.214$, or group, $F(1,55)<1$. In addition, no two-way interactions reached significance: trial type by group, $F(1,55)<1$, trial type by laterality, $F(1,55)<1$, and group by laterality, $F(1,55)=2.48$, $p=.121$. The three-way interaction approached, but did not reach, significance, $F(1,55)=3.19$, $p=.080$.

*P3.* A 2 (trial type) by 2 (ROI site) by 2 (group) repeated-measures ANOVA indicated a significant main effect of trial type on P3, $F(1,55)=12.71$, $p=.001$, $\eta_p^2=.188$, such that the SST yielded a larger P3 component than the USST. This trial type effect differed significantly by ROI site, $F(1,55)=6.74$, $p=.012$, $\eta_p^2=.109$, with post-hoc analyses indicating that the magnitude of the trial type effect (i.e., SST>USST) was significantly larger at the anterior site than the posterior site, $t(56)=2.48$, $p=.016$. The interaction of trial type and group approached significance, $F(1,55)=3.261$, $p=.076$, with the magnitude of the trial effect being larger in the RB group than in the TDC group. There were no effects of group and ROI site, nor an interaction of group and ROI site, $F(1,55)<1$ for each. In addition, the three-way interaction did not reach significance, $F(1,55)=1.102$, $p=.298$.

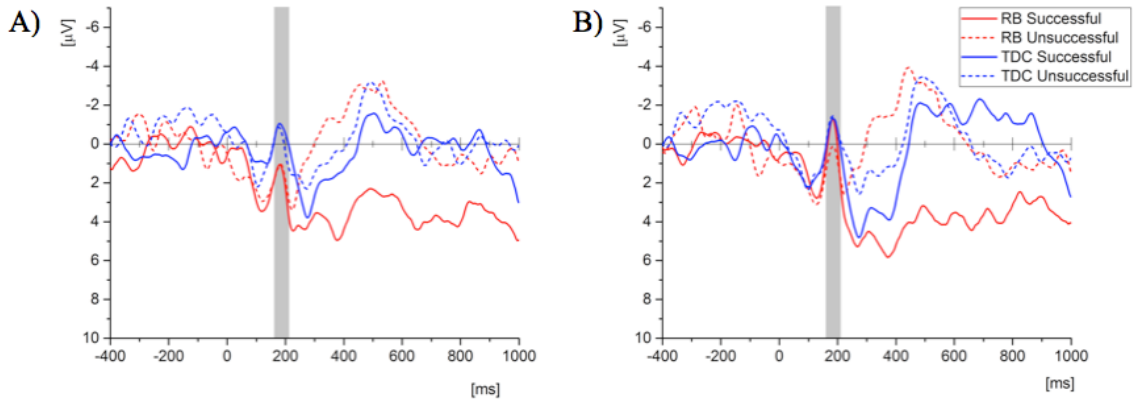


Figure 9

*ERP Waveforms by Group for N2 in the Stop-Signal Task*

Waveforms for successful and unsuccessful trials by group in the (a) left and (b) right N2 ROIs.

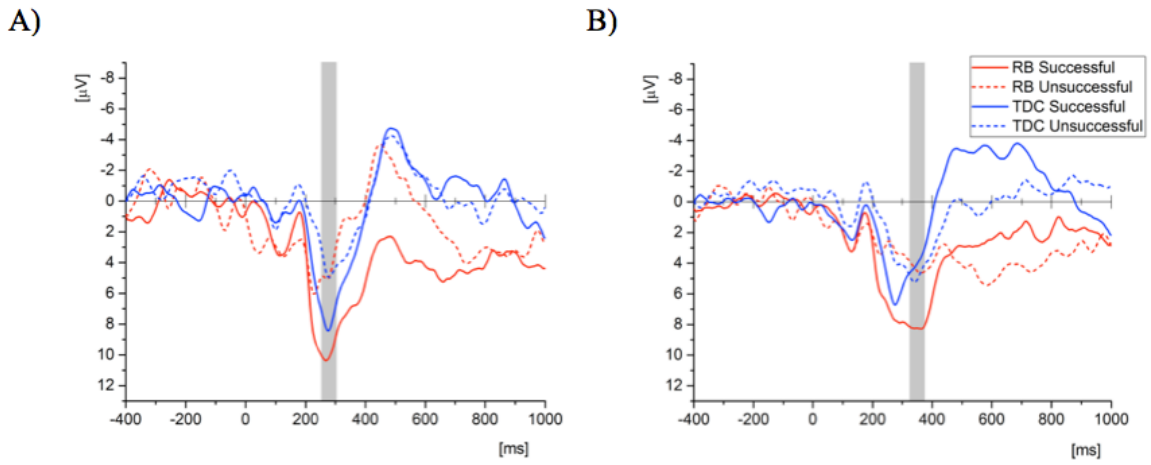


Figure 10

*ERP Waveforms by Group for P3 in the Stop-Signal Task*

Waveforms for successful and unsuccessful trials by group in the (a) anterior and (b) posterior P3 ROIs.

***Effects of Age***. To examine the role of age on indicators of conflict monitoring and conflict resolution during motor inhibition, ERP data were first analyzed continuously. Correlations between age and ERP component (N2, P3) amplitude were not significant for either trial type and at either ROI. The potential relationship between age and ERP amplitude was further examined by exploring ERP amplitude across four age bins: 10-11 year-olds (N=14), 12-13 year-olds (N=20), 14-15 year-olds (N=13), and 16-17 year-olds (N=10). ERP waveforms are presented by age in Figure 11.

*N2.* A 2 (trial type) by 2 (laterality) by 4 (age) repeated-measures ANOVA indicated no main effects of trial type, $F(1,53)<1$, laterality, $F(1,53)=1.57$, $p=.216$, or age, $F(3,53)<1$, on N2 amplitude. Interactions of age with trial type, $F(3,53)<1$, and laterality, $F(1,53)<1$, were both insignificant, as was the trial type by laterality interaction, $F(1,53)<1$, and the three-way interaction of trial type, laterality, and age, $F(3,53)=1.36$, $p=.071$.

*P3.* The omnibus ANOVA on P3 amplitude indicated a main effect of trial type, $F(1,53)=11.19$, $p=.02$, $\eta_p^2=.174$, such that the P3 was larger on SSTs than USSTs. This effect varied as a function of ROI, $F(1,53)=4.01$, $p=.050$, $\eta_p^2=.070$, again indicating that the magnitude of the effect was larger at the larger at the anterior site than the posterior site, $t(56)=2.48$, $p=.016$. There was no main effects of laterality, $F(1,53)<1$, or age, $F(3,53)<1$ on P3 amplitude, nor were there significant interactions between age and trial type, $F(3,53)<1$, or age and ROI, $F(3,53)=1.15$, $p=.339$. The three-way interaction of age, trial type and ROI on P3 amplitude also did not reach significance, $F(3,53)=2.10$, $p=.111$.

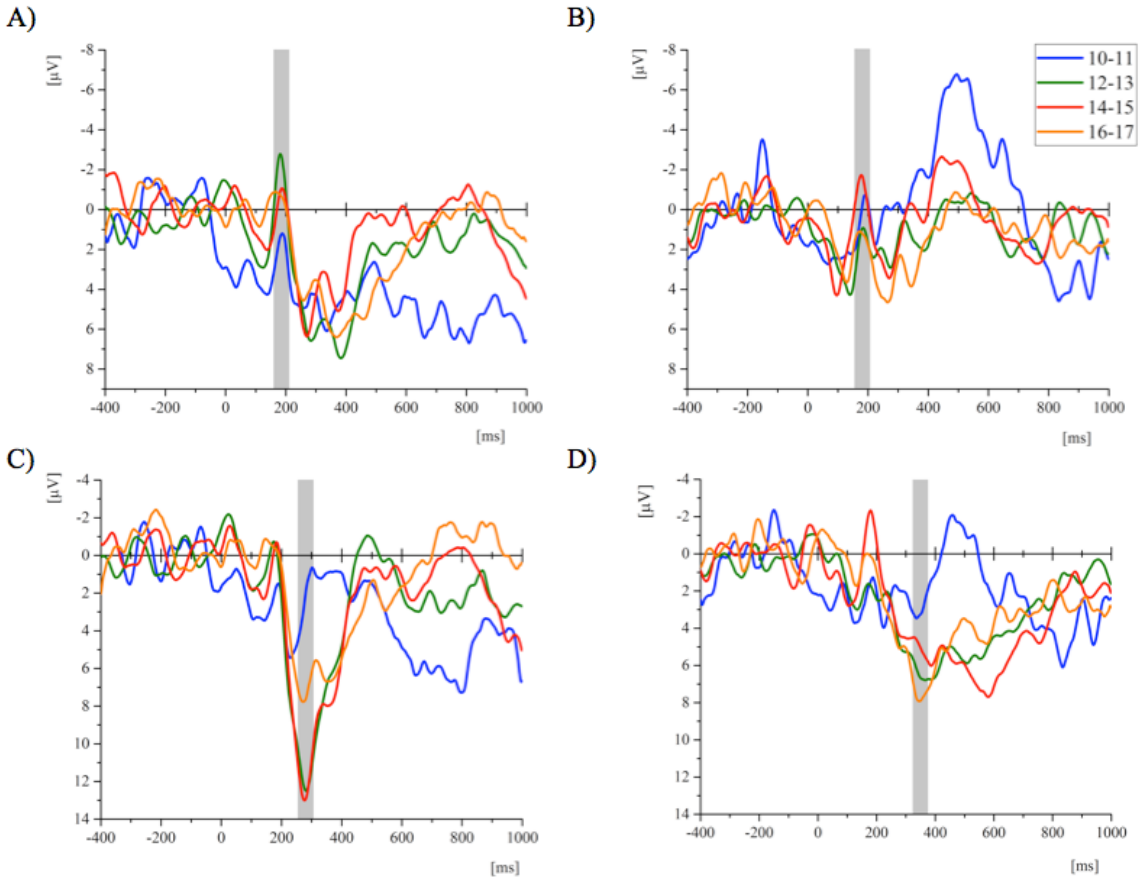


Figure 11

*ERP Waveforms by Age for the Stop-Signal Task*

Waveforms for N2 are presented by age at the right ROI for (a) successful and (b) unsuccessful trials. Waveforms for P3 are presented by age at (c) the anterior midline ROI for successful trials and (d) the posterior midline ROI for unsuccessful trials.

# Chapter 4

# DISCUSSION

Phenotypic presentations of RBs, seen throughout the DSM-V, naturally lend to the idea of associated difficulties with behavioral inhibition. In line with NIMH's RDoC initiative to better capture mechanisms of dysfunction associated with psychopathology, the present study extended inhibitory control research, focused primarily on OCD and TTM, to examine indicators of inhibitory control dysfunction that were common to, and/or distinct in, neurodevelopmental repetitive behavior disorders. Embedded within the aims were questions regarding whether inhibitory control could be viewed as a unidimensional construct, either within stages of control and/or to contexts in which control is taxed, and if any precise deficits were universal across repetitive behaviors.

Despite observing well-established effects of each task's respective ERP components and performance measures, the results largely disconfirmed hypotheses that individuals with neurodevelopmental RBs differed from controls in measures of inhibitory control tapped by the two procedures employed in the current study. However, there is some evidence of the specificity of inhibitory control difficulties by stage of control and context, as well as a potential area of weakness in attention-based conflict resolution in individuals with neurodevelopmental RBs. When compared to research on other RBs, these data contribute to a growing body of work aiming to more

comprehensively understand the relationships across RBs for the larger purpose of informing diagnostic classifications and treatment.

## Validity of ERP and Performance Measures

The present study employed two well-documented paradigms (i.e., EFT for interference control, Stop-Signal Task for motor inhibition), each of which allowed for the collection of ERP-related correlates of conflict monitoring and conflict resolution, as well as performance data reflecting behavioral efficiency. The validity of data was established through examination of the expected within-person effects.

### Conflict Monitoring Measures

Functionally tied to the ACC, conflict monitoring is a critical early stage in the process of inhibitory control that is reflected in a family of ERP components. In the tasks of the current study, conflict monitoring was investigated across two contexts: interference control (i.e., ERN) and motor inhibition (i.e., N2 component).

Throughout the literature, the amplitudes of conflict monitoring components are reliably larger when participants make erroneous (versus correct) responses (i.e., ERN), receive negative (versus positive) feedback on learning trials (i.e., feedback-related negativity [FRN]; Simons, 2010; Yeung et al., 2004), and unsuccessfully (versus successfully) inhibit motor responses (i.e., N2; Liotti et al., 2005). In fact, unsuccessful motor inhibition appears to be functionally similar to other erroneous responses insofar as the participant is unable to assemble sufficient control to inhibit a dominant response. Accordingly, the frequently observed increase in N2 amplitude on USSTs parallels the ERN, whereas the N2 amplitude on SSTs parallels the CRN. The functional overlaps of

these components, coupled with their common neural generation in the ACC (e.g., Botvinick et al., 2001; van Veen & Carter, 2002), suggests the categorization of the ERN fits within Kok's (1986) conceptual framework to indicate that ACC-modulated ERP components serve as "flags" of conflict detection and indicate the need for resolution.

Consistent with the literature, the ERN in the present study was observed with a fronto-central midline scalp distribution approximately 50 ms following erroneous responses. It was reliably larger than the CRN in the unadjusted data, as well as following application of Woody filter procedures. Further, behavioral data indicated that RTs were shorter on erroneous responses, and incongruent trials elicited longer RTs and lower accuracy than congruent trials. A decrease in post-error accuracy was also observed, which has been observed in a number of other studies (e.g., Hajcak & Simons, 2008; Hajcak et al., 2003).

The N2, as predicted, was observed with a lateralized, anterior distribution about 200 ms after the presentation of the stop-signal. Although the laterality effect (i.e., right > left) did not reach significance in this particular study, it trended in the direction consistent with literature. Given the increased level of conflict on USSTs, results of stop-signal tasks frequently find that the N2 is larger on USSTs than SSTs (Kok et al., 2004; Krompinger, 2011; Pliszka, Liotti, & Woldorff, 2000; Ramautar, Kok, & Ridderinkhof, 2006). The present study found no significant difference in the N2 between SSTs and USSTs across all participants. While the reasons for this lack of this expected effect are unclear, it has been observed in at least one previous study from the same laboratory (Katona, 2012).

Taken together, research supports the view that ERN and N2 components reflect comparable conflict monitoring processes in their respective contexts. Within-person ERP and behavioral effects were achieved as expected in the EFT. Although the expected N2 amplitude differentiation between USST and SST was not observed in the Stop-Signal Task, the expected latency and topographical distribution of the N2 were achieved. Both the ERN and N2 therefore appear to be valid assessments of conflict monitoring.

**Conflict Resolution Measures**

Following the ERN and N2 are the Pe and frontal, no-go P3, respectively, both of which are purportedly involved in task-specific forms of conflict resolution. Some researchers have conceptually linked the two ERP components, citing both as being enhanced to higher degrees of conflict, such that the Pe is larger to erroneous trials than correct trials, and the P3 is larger for stop-trials than go-trials (e.g., Overtoom et al., 2002).

However, principle components analysis identified that the Pe waveform is, in fact, composed of two components: an earlier, evaluative component (i.e., frontocentral positivity following the ERN) and a later, attention-based component (i.e., parietal, P300-like positivity; Arbel & Donchin, 2009). Given the topographic and functional similarities, the Pe has been more closely likened to the P3b, analogous to the P3 to USSTs, which functions in context-updating.

In contrast to the evaluative nature of the Pe, which occurs *following* an erroneous response, the no-go P3 occurs in response to the stop-signal-locked at roughly the same latency and therefore appears to reflect a more *online* assessment of conflict resolution.

The distinctions between the Pe and no-go P3 can be reconciled as distinct ways in which conflict is resolved in their given contexts. In the context of interference control, inhibitory control is required primarily in the attentional domain, and accordingly, the Pe functions in processing the attention-based conflict salience (Falkenstein et al., 2000; Moser et al., 2005). In the context of motor inhibition, inhibitory control is required primarily in the behavioral domain, and the no-go P3 functions as the "brake" in Polich's (2007) neuroinhibition model of the P3a, reflecting the strength of conflict resolution during the inhibition process.

Observed within-person effects for these two components were consistent with the literature. The Pe was present at central-parietal midline sites about 200 ms following an erroneous response. The positivity was significantly larger following errors than correct responses using both unadjusted and Woody filtered analysis procedures.

In the Stop-Signal Task, the no-go P3 occurred earlier and with a more frontally-distributed topographic distribution than did the P3 associated with USSTs. This pattern of latency and topography is consistent with previous studies (Dehaene et al., 1994; Herrmann et al., 2004). Further, the amplitude of the no-go P3 was enhanced relative to that of USSTs, reflecting focused attention on facilitating the suppression of the prepotent response. RTs, including the duration of SSRTs observed, and the shorter SSDs for successful trials than unsuccessful trials, were also consistent with previous studies (Logan & Cowan, 1984; deJong, 1990).

Collectively, research supports the view that the Pe and no-go P3 are related to task-specific goals of conflict resolution. Within-person ERP and behavioral effects were

achieved as expected across both the Pe and no-go P3, indicating that both appear to be valid assessments of conflict resolution.

## Specificity of Inhibitory Control Deficits

Following confirmation of expected within-person effects, these measures were used to identify any deficits associated with neurodevelopmental RBs, while simultaneously assessing the specificity and universality of inhibitory control dysfunction. ERP measures were visually conceptualized within a 2 (stages of inhibitory control) x 2 (contexts of inhibitory control) matrix, such that four domains of potential inhibitory control deficits were examined. Between-group reflections on each of these areas of specificity, incorporating associated performance measures, provide some evidence that inhibitory control is not a unidimensional construct, but rather shows specificity based on interactions of stage of conflict and context, and suggests that neurodevelopmental RBs may be associated with a specific inhibitory control weakness.

### Conflict Monitoring During Interference Control

Despite BG- and ACC-related deficits in TD and ASD fueling the hypothesis that the RB group would be associated with reduced conflict monitoring in the context of interference control, the RB group demonstrated ERN comparable to controls. This null finding was reconciled with extant literature yielding inconsistent findings in TD and ASD with several reporting null ERN results (e.g., Eichele et al., 2016; Groen et al., 2008). Groups also did not differ on performance measures. The present data support findings that inhibitory control may, in fact, not be associated with impairment in conflict monitoring during interference control tasks.

**Conflict Monitoring During Motor Inhibition**

The hypothesis that the N2 to USSTs would be attenuated in the RB group was disconfirmed. While an overall smaller N2 was observed in the RB group on both USSTs and SSTs in the left ROI, and on USSTs in the right ROI, these effects did not reach significance. This trend does reflect the pattern of results observed in the only known study looking at the N2 in one of the targeted RB disorders (ASD), which found the N2 to be significantly smaller on high-conflict trials (i.e., analogous to USSTs) than low-conflict trials (Larson et al., 2012). However, as the results of the present study were not significant, we are, at present, unable to claim that neurodevelopmental RBs are associated with conflict monitoring deficits in the context of motor inhibition.

**Conflict Resolution During Interference Control**

Given the inconsistent literature on the Pe's relationship to psychopathology, a clear hypothesis for RB's relationship to the Pe had not been established. However, the results indicated that RB group, relative to the TDC group, had a smaller magnitude differential between the positivity following erroneous and correct responses. These results should be interpreted with caution, as the Pe's relationship with psychopathology is evanescent in literature. In fact, studies of interference control testing populations that comprised our RB group have yielded null results to this point (e.g., Eichele et al., 2016; South et al., 2010).

However, this finding warrants follow-up as to why the present RB group may have elicited such an effect. If replicated, the potential implications are twofold. First, the data support work on OCD (Gehring et al., 2000; Hajcak & Simons, 2002; Santesso et al.,

2006), indicating that inhibitory control is not a unidimensional construct, but instead that inhibitory control deficits may be specific to an interaction between the stage of control (e.g., for neurodevelopmental RBs, conflict resolution) and the context in which control is taxed (e.g., interference control). Second, as the Pe is postulated to reflect awareness and salience of the outcome, these data purport that individuals with RBs may have increased difficulty subjectively differentiating error and correct responses. In other words, their awareness of correct and erroneous responses is comparable, indicating that errors are less salient.

### Conflict Resolution During Motor Inhibition

The hypothetical relationships that the RB group would have attenuated no-go P3s and longer SSRTs, relative to the TDC group, were not observed. As such, the data suggest that the RB group assembled a comparable amount of neuroinhibitory resources in order to inhibit a prepotent response with the same degree of efficiency as healthy controls. Behavioral deficits in TD and ASD groups have been observed in some previous studies, although this result has not been entirely consistent (Li, Huang, Constable, & Sinha, 2006; Ozonoff et al., 1994; Roessner et al., 2008). Further, although TD and ASD populations have demonstrated decreased DLPFC volume and poor behavioral performance in past studies, ERPs correlates are lacking at present, leading to difficulty with reconciliation of the present results.

## Toward a Dimensional Understanding of Inhibitory Control across RBs

Despite well-established procedures eliciting expected within-subject ERP components and performance differences, the RB group largely exhibited levels of

inhibitory control comparable to controls. Although there is some indication of a specific interference control deficit within the conflict resolution stage of inhibitory control, this finding must be interpreted with caution. Through comparison of these data to that of other RBs with more established inhibitory control deficits, we not only glean information about why effects may not have been observed in the present study, but can also integrate this information to better understand the relationships among RBs.

**Specificity of Inhibitory Control Dysfunction Across RBs**

Thus far, OCD has been the most well-studied of RB presentations and has consistently been associated with increased ACC activity (Baxter et al., 1987; Ursu et al., 2003) and heightened conflict monitoring in interference control contexts (Gehring et al., 2000). However, its deficits are not universal across interference control, as inconsistent results have been reported with Pe (Gehring et al., 2000; Hajcak & Simons, 2002; Santesso et al., 2006), nor are they universal to the conflict monitoring stage of control across contexts, as inconsistent results have been reported with N2 during motor inhibition (Kim et al., 2007; Ruchsow et al., 2007). Thus, it appears that there may be specificity to inhibitory control deficits, dependent upon the stage of control and the context in which control must be exerted.

TTM, on the other hand, has more often been associated with *hypo*activity of conflict-related brain structures (Chamberlain et al., 2008; Fitzgerald et al., 1999; Keuthen et al., 1996; O'Sullivan et al., 1997) and was observed to have decreased conflict monitoring in an interference control task (Roberts et al., 2014). As in OCD,

results did not extend to other stages of inhibitory control within the same task, and TTM has thus far not elicited consistent findings in other contexts.

In comparison to OCD and TTM, which most consistently show deficits in conflict detection stage of interference control, the present study found intact conflict monitoring in individuals with neurodevelopmental RBs. Instead, a potential deficit was observed in the conflict resolution stage of interference control. Collectively, the specificities of inhibitory control dysfunction for each RB presentation provide evidence of the utility of ERPs in teasing apart specific maladaptive aspects of inhibitory control.

**Relationships in Inhibitory Control Among RBs**

It is also notable that the precise pattern of inhibitory control dysfunction varies across different RB presentations, particularly when considering the overlaps in comorbidity, neurobiology, and phonemonology that lend to the idea that they are not entirely distinct, as is suggested by the DSM-V. At the symptom level, the RBs associated with TD and TTM appear to hang together in the sense of that they are preceded by premonitory urges and followed by feelings of relief (Himle et al., 2007). While ASD is characterized by a similar level of impulsivity in many of its repetitive behaviors, there are also other aspects like ridigity (i.e., repetitive thoughts) that differentiate it at a symptomatic level. OCD appears distinct from the aforementioned presentations in the thoughts (obsessions) that precede the repetitive behaviors performed in response to the thoughts (compulsions; American Psychiatric Association, 2013).

Looking across units of analysis, physiological studies demonstrate that brain regions associated with inhibitory control are, at least at times, dysfunctional in these

presentations. OCD is set apart from the other presentations in its hyperactive ACC (Baxter et al., 1987; Ursu et al., 2003), whereas TTM, TD, and ASD are most often associated hypoactive ACC activity (Agam et al., 2010; Chamberlain et al., 2008; Muller-Vahl et al., 2009). While there is less research on DLPFC and OFC activations to allow for comparison across these presentations, behavioral studies provide evidence of performance deficits in each RB that may be associated with dysfunction in these brain areas. Interestingly, TTM has been associated with more deficits in motor inhibition than OCD (Chamberlain et al., 2006), providing some support for increased impulsivity in this group. It is notable that TD, relative to other presentations, has less consistently been linked to behavioral deficits (Li et al., 2006; Roessner et al., 2008).

The observed discrepancies in inhibitory control across psychophysiological measures appear to fit a model proposed by Hollander (1993), conceptualizing the relationship between OCD and TTM. Specifically, Hollander theorized that a continuum exists between impulsivity/risk-seeking behaviors and compulsivity/risk-aversive behaviors, such that TTM falls toward the impulsive end of this spectrum, and OCD falls toward the compulsive end. Psychophysiological data, in terms of both ACC/BG activation and ERN, appear to both support Hollander's dimensional conceptualization of these presentations, as well as extend his model to suggest that impulsivity may be characterized by an undermonitoring of one's behaviors (i.e., reduced ERN in TTM), while compulsive behavior may be characterized by attention-based overmonitoring of one's behaviors (i.e, heightened ERN in OCD). Further supporting Hollander's model are psychophysiological data from related psychopathologies, finding that presentations

associated with impulsivity (e.g., ADHD, psychopathy; Allen & Dikman, 1998; Shiels & Hawk, 2010) have psychophysiological presentations that resemble TTM, and presentations associated with worry and risk avoidance more closely resemble OCD (Hajcak, McDonald, & Simons, 2003a; Hajcak & Simons, 2002; Moser et al., 2012).

Based on ERN and N2 data collected in this study, neurodevelopmental RB disorders appear to fall in between TTM and OCD on this continuum. They demonstrated neither heightened, nor reduced, levels of conflict monitoring across the two tested contexts, and they had behavioral performance comparable to the control group. Interestingly, their psychological profiles, as measured through parent-report questionnaires, indicated both increased compulsivity and impulsivity relative to controls. As these factors may "pull" individuals towards both the compulsive and impulsive sides of Hollander's spectrum, it is curious of the combination of these traits potentiate behavior that appears typical to that of healthy controls.

The present findings for the Pe are tentative, as are the relationships of other RBs to measures of conflict resolution across contexts. Further research will be needed to ascertain, with consistency, the relationships of Pe and stop-trial P3 components to RBs prior to integrating conflict resolution into the conceptual model linking these RBs.

**If Not Inhibitory Control, Then What?**

The largely insignificant findings in the present study suggest that inhibitory control, as tapped by the tasks in the present study, is not impaired. This begs the question, then, as to what other domains of dysfunction may be contributing to these maladaptive RB presentations. Based on the finding in this study that individuals may

struggle with inhibitory control in the context of an attention-based paradigm, attention itself may be one area of further exploration. Given that tics, like hairpulling, can present as both focused (i.e., within one's awareness) and unfocused (i.e., outside of one's awareness; American Psychiatric Association, 2013), attention may serve as a moderator in assessment of these groups. Other RDoC domains that warrant further research are habits (given the repetitive, and sometimes habit-like, nature of RBs), action selection (given conscious decision to engage in some RBs), reward valuation (given relief that follows some RBs), and reward learning (given the reinforcing pattern of some RBs). Many of these domains of functioning are associated with the same brain regions as inhibitory control and thereby would account for the structural and functional neuroimaging differences observed in the ACC and BG in these populations. Looking at these domains of functioning both within neurodevelopmental RBs, as well as other RBs like OCD and TTM, will expand our understanding of these relationships among these presentations.

## Strengths and Limitations of the Present Study

The study evinced a number of strengths. For one, the use of temporally sensitive ERP methodology allowed inhibitory control to be parsed into constituent substages that occur relatively closely in time. Further, through the use of two well-established paradigms, each of these substages were explored in two contexts, allowing for the examination of whether inhibitory control dysfunction was specific to substages, contexts, or an interaction of both. As such, it provided valuable knowledge as to the specificity of inhibitory control deficits.

A second strength of this study was that it is representative of, and generalizable to, the population of individuals who struggle with these repetitive behaviors, in terms of its gender distribution and psychopathological comoribidities. With regard to gender, the gender ratio of ASD is considered 4-5:1 males to females (Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014), although there is concern that males may be more readily diagnosed due to gender-specific mutations, protective factors in females, and criteria that are more oriented to males (c.f., Jeste & Geschwind, 2014; c.f., Werling & Geschwind, 2013). Comparably, large-scale studies of TD have similarly found a male-female gender ratio of 4.3:1 (Freeman et al., 2000). In the present study, male-to-female gender ratios were 10.2:1 in the EFT and 4.7:1 in the Stop-Signal Task. While the sample in the EFT had a higher percentage of males than in the general population, that of the Stop-Signal Task is relatively consistent with the general population, and both reflect the significant gender difference in the prevalence of these RB presentations.

The psychological complexity associated with the RB group also appeared to accurately reflect the larger population of TDs and ASDs. Epidemiological studies have yielded that 71% of individuals with ASD and 88% of individuals with TD had at least one psychological comorbidity (Freeman et al., 2000; Simonoff et al., 2008). For ASD, the most common comorbidities are ADHD (29%), ADHD (28%), and oppositional defiant disorders (28%; Simonoff et al., 2008). On average, individuals with TD have two comorbidities, the most common of which were ADHD (60%), OCD (27%), mood disorders (20%), and anxiety disorders (18%; Freeman et al., 2000). Although rates of

some comorbid diagnoses reported by individuals in our sample are lower than these prevalence rates, the symptom presentations measured through questionnaires capture more elevated, perhaps undiagnosed, levels of comorbidity and thus appear to be an accurate representation of the relevant populations.

Relatedly, analyses of the psychological characteristics of included versus excluded participants revealed that included participants provide a fairly accurate representation of the recruited samples in both tasks. It is notable that individuals in the RB group displayed fewer repetitive behaviors in some domains, and therefore may represent a less severe, but still clinical, sample of individuals with TDs and ASD. In contrast, included TDC participants in the Stop-Signal Task displayed higher levels of several executive function difficulties than those excluded. Taken together, although the included subsets may have less differentiation across a few domains of RBs and executive function that could possibly mitigate effects, the levels of disorder-specific RBs for participants included in the RB groups remain at clinical levels, and executive functions of the TDC group remain in the normal range. Psychological characteristics of included and excluded participants are otherwise largely similar, indicating that the included subset of the sample is fairly representative of the larger, recruited sample.

A third strength of this study was the exploratory application of a novel version of the Woody filtering technique. This technique was initially designed for alignment of the P3 (Woody, 1967) and was recently adjusted for application to the ERN (Lin, Gavin, & Davies, 2015). In its nascent state, it has not yet been carefully vetted and was applied for exploratory purposes in the present analyses. As per visual inspection of Figure 3, the

technique, indeed, yielded more pronounced ERN and CRN waveforms, and consistent with unadjusted results, yielded a significant overall ERN-CRN differentiation, suggesting that the adjustment technique may be promising. It is unclear if support for this technique may also have found in the effects of age on the ERN. While Woody filtered results more closely supported literature (Segalowitz & Davies, 2004) than unadjusted results, the extent to which ERN amplitude increases with age may warrant reconsideration following application of this latency-correction method (Wiersema, van der Meere, & Roeyers, 2007).

There were several limitations to the study as well. For one, the RB group was comprised of predominately of individuals with ASD relative to TD (70% ASD in EFT; 75% ASD in Stop Signal Task) due to TD-specific difficulties with recruitment. This created increased heterogeneity within the group, such that a higher proportion had ASD-specific repetitive behaviors, as well as comorbid social/communication difficulties.

Second, although the RB group presented with psychological complexities that were representative of the larger population, several of these comorbidities have known effects on ERP components targeted in this study (e.g., Gehring et al., 2000; Hajcak et al., 2004; Liotti et al., 2005). The most notable of these is OCD. Although individuals were excluded for a diagnosis of OCD or a parent-reported history of OC symptoms at the time of the phone screen, parent-reported questionnaires yielded heightened levels of OC symptoms in the RB group relative to the control group. While it is possible that comorbid OC-symptoms may have increased the amplitudes of several ERP components, it is notable that the RB group also exhibited heightened levels of impulsivity and

depressive symptoms, which typically attenuate the same components (Krompinger, 2011; Shiels & Hawk, 2010) and may have counteracted any OC-driven effects. Ideally, incorporation of group with heightened levels of anxiety and executive function difficulties into the study would assist in ascertain the effects that are related to RBs above and beyond comorbid psychopathology.

A third limitation is that inherent within the population of RBs are involuntary motor movements, which create more muscle activity. Such movement is likely further exacerbated in this group by the presence of other executive function difficulties. Despite increased breaks, visual inspection of the data indicated that these movements increased noise and artifacts in each trial, leading to greater trial rejection via automatic artifact rejection, and hence fewer trials included in individual grand averages.

## Implications and Final Conclusions

NIMH's RDoC initiative is moving the field toward a more comprehensive understanding of dimensions of functioning, through examinations of presentations ranging from typical to atypical, for the larger purpose of informing diagnosis and treatment. The present study has implications in diagnosis, in terms of understanding inhibitory control dysfunction across RB presentations, as well as in treatment considerations for individuals with neurodevelopmental RBs.

Diagnostically, the present data support previous research on OCD and TTM indicating that inhibitory control deficits are not unidimensional, but rather demonstrate specificity to the stage of control and the context in which it is taxed. Although the specific deficit identified in neurodevelopmental RBs should be interpreted with caution,

it remains clear that this group does not exhibit the same pattern of inhibitory control deficits that is seen in OCD or TTM. This suggests that the phenotypic similarities of RBs, as well as the heightened levels of comorbidities seen across these presentations, may not be related to common inhibitory control deficits, at least as tapped by the two tasks employed in the current study. Further research is therefore needed to better understand the relationships among these RBs, in ways such as testing inhibitory control in other contexts and exploring other areas of potential mechanisms of dysfunction.

When applied to treatment, the different specificities to inhibitory control dysfunction present across RBs suggest that the same treatment modules may not be equally effective for all RB presentations. For OCD and TTM, the difficulties manifest at the conflict monitoring stage of inhibitory control during interference control, whereas, deficits in neurodevelopmental RBs may be associated with conflict resolution during interference control. Should the present study's results hold in further research aimed to reconcile inconsistent findings, it may suggest individuals with neurodevelopmental disorders have difficulty differentiating the urge to perform the RB from extraneous noise (e.g., physical sensations, thoughts), which may in turn perpetuate the RBs. It is also likely that this inhibitory control deficit manifests in other contexts requiring interference control, contributing to impairment across domains of functioning. In consideration of treatment modules, the precise area of inhibitory control dysfunction identified suggests that individuals with neurodevelopmental RBs may benefit from treatment modules aimed to increase awareness of the conflict and/or increased motivation work to increase the salience of the conflict.

In conclusion, the present study addressed the need for further research clarifying the relationships among psychological presentations characterized by repetitive behaviors. While results largely indicated that individuals with neurodevelopmental RBs did not differ from healthy controls in terms of the inhibitory control areas tapped by the two procedures used in the present study, it did provide additional support that inhibitory control deficits are neither unidimensional nor universal. Rather, they reflect specificity to stage of control and context that appears to vary across RBs. Further work focused on identifying specific, and perhaps alternative, mechanisms of dysfunction within and across RB presentations will continue drive diagnosis to be more precise, and consequently, treatments to be more effective.

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# Appendix A

## CHILDREN'S HOSPITAL OF PHILADELPHIA INSTITUTIONAL REVIEW BOARD APPROVAL


The Children's Hospital of Philadelphia®
RESEARCH INSTITUTE

INSTITUTIONAL REVIEW BOARD

**Date:** August 17, 2015

**To:** John Herrington
**CC:** Kathryn Lowe
**From:** The Committees for the Protection of Human Subjects (IRB)

**Re:** IRB 13-010318, **Protocol Title:** Psychophysiological Correlates of Inhibitory Control in Trichotillomania, Chronic Tic Disorder, and Autism
**Sponsor or Funder**: Children's Hospital of Philadelphia, The (CHOP), University of Delaware

**IRB CONTINUING REVIEW: NOTICE OF IRB APPROVAL**

Dear Dr. Herrington,

The progress report for the study referenced above was reviewed and approved by Dr. Barbara Engel, Chair of the IRB (or her authorized designee) on 8/17/2015 using expedited procedures as set forth in 45 CFR 46.110/21 CFR 56.110.

Approval is effective as of August 17, 2015. The study will expire on August 16, 2016.
The study is approved to enroll 200 subjects from CHOP with a total enrollment study wide of 200.

**Main Study Documents:**

- Protocol (dated 10/20/2014)
- Main Consent Form (dated 3/13/2014)
- Verbal Screening ICF (dated 6/25/2013)

Please refer to the eIRB application for a complete list of all documents submitted to the IRB.

**IRB Determinations:**

- Expedited Category: 45 CFR 46.110, Category 4, 5, 6, & 7
- Subpart D Determination: 45 CFR 46.404 or 21 CFR 50.51

**Consent/Assent/HIPAA:**

- **Consent Form:** Written consent/assent/HIPAA authorization are required for study enrollment. The approved, date-stamped informed consent document is available in the main study workspace under the IRB Correspondence tab.

3535 Market Street, Suite 1200, Philadelphia, PA, 19104
Tel: 215-590-2830
Email: IRBOffice@email.chop.edu
Website: https://irb.research.chop.edu/

- **Waiver Of Documentation Of Consent/HIPAA:** The criteria under 45 CFR 46.117(c)(2) are met for waiver of documentation of consent. In addition, the criteria under 45 CFR 164.512(i)(2)(ii) are met for an alteration of HIPAA authorization (to obtain verbal authorization) for screening purposes.

Please note the following conditions for conducting this study:

**INVESTIGATOR RESPONSIBILITIES:** Please refer to the following page on the IRB's website for information and guidance on the responsibilities of investigators who conduct human subjects research at CHOP: https://irb.research.chop.edu/investigator-responsibilities.

**REPORTABLE EVENTS:** On-site reportable events, that occur in relation to this study, such as serious adverse events, protocol deviations/violations, unanticipated problems involving risk to subjects or others, and non-compliance must be reported promptly to the IRB, as outlined in IRB SOP 408. Please refer to the following page on the IRB's website for information about reportable events: https://irb.research.chop.edu/reportable-events.

**RENEWAL (Continuing Review/Progress Reports):** Approval is valid until the expiration date for your protocol shown above. The IRB must review and approve all human subject research studies at intervals appropriate to the degree of risk. To avoid lapses in study approval and suspension of study procedures, please submit the application for continuing review at least 45 days before the expiration date for your protocol. This will provide the IRB will sufficient time to review your study. As a courtesy, the IRB will send you a reminder; however, it is your responsibility to ensure that you submit the continuing review application on time.

**CHANGES/AMENDMENTS/MODIFICATIONS/REVISIONS:** You must obtain IRB review and approval under 45 CFR 46 / 21 CFR 50, 56 if you change any aspect of this study, including but not limited to study procedures, consent form(s), co-investigator, study staff, advertisements, protocol document or procedures, Investigator's Brochure or accrual goals. Implementation of these changes cannot occur until you receive the IRB approval notice.

**COMPLETION OF STUDY**: Notify the IRB when your study is completed. Neither study closure by the sponsor nor the investigator removes your obligation for submitting a timely continuing review or a final report.

If you have any questions, please click on the IRB# (above) and contact the IRB analyst listed in the continuing review work space.

**DHHS Federal Wide Assurance Identifier: FWA0000459**

CR_017a **** *This memorandum constitutes official CHOP IRB correspondence.* ****

3535 Market Street, Suite 1200, Philadelphia, PA, 19104
Tel: 215-590-2830
Email: IRBOffice@email.chop.edu
Website: https://irb.research.chop.edu/

## Appendix B

## UNIVERSITY OF DELAWARE INSTITUTIONAL REVIEW BOARD APPROVAL

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
*Ph:* 302/831-2136
*Fax:* 302/831-2828

DATE: September 3, 2015

TO: Kathryn Roberts, M.A.
FROM: University of Delaware IRB

STUDY TITLE: [536489-3] Psychophysiological Correlates of Inhibitory Control in Trichotillomania, Chronic Tic Disorder, and Autism

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED
APPROVAL DATE: September 3, 2015
EXPIRATION DATE: August 16, 2016
REVIEW TYPE: Administrative Review

REVIEW CATEGORY: *Adminstrative Review- CHOP IRB is the IRB of Record for this Project.*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Administrative Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.