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Cognitive Set Shifting Deficits and Their Relationship to Repetitive Behaviors in Autism Spectrum Disorder

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Abstract

The neurocognitive impairments associated with restricted and repetitive behaviors (RRBs) in autism spectrum disorder (ASD) are not yet clear. Prior studies indicate that individuals with ASD show reduced cognitive flexibility, which could reflect difficulty shifting from a previously learned response pattern or a failure to maintain a new response set. We examined different error types on a test of set-shifting completed by 60 individuals with ASD and 55 age- and nonverbal IQ-matched controls. Individuals with ASD were able to initially shift sets, but they exhibited difficulty maintaining new response sets. Difficulty with set maintenance was related to increased severity of RRBs. General difficulty maintaining new response sets and a heightened tendency to revert to old preferences may contribute to RRBs.

Keywords

Cognitive flexibility; Insistence on sameness; Repetitive behavior

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Introduction

Autism spectrum disorder (ASD) is defined by two core features: (1) persistent deficits in social-communication, and (2) restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association 2013). Relative to social-communicative abnormalities, restricted and repetitive behaviors (RRBs) have received considerably less research attention, despite being perhaps the most distressing aspect of the disorder for parents and affected individuals and the primary target for medication therapies (Brown et al. 2012; Gordon 2000; Kuhlthau et al. 2010). Clarifying the neurocognitive bases of these behaviors is important for both identifying neurophysiological mechanisms associated with ASD and determining selective targets for behavioral and pharmacological treatments.

Studies aimed at identifying the neurocognitive processes underlying RRBs in ASD have implicated broader executive dysfunctions, but more specific cognitive alterations associated with RRBs have not been consistently identified (Kenworthy et al. 2008; Leekam et al. 2011; Lopez et al. 2005; Mosconi et al. 2009; Ravizza et al. 2013). One candidate mechanism is cognitive inflexibility, or the reduced ability to modify a cognitive rule to guide behavioral choices and meet changing environmental demands (Turner 1997). Individuals with ASD have been shown to be impaired in their ability to switch from one learned rule to a new rule in response to changing behavioral contingencies—a process referred to as set shifting (Corbett et al. 2009; Geurts et al. 2009; Kaland et al. 2008; Ozonoff 1995; Ozonoff et al. 2004; Pellicano 2010; South et al. 2007; Yerys et al. 2009). Yet, other studies have suggested that set shifting abilities in individuals with ASD are relatively spared (Geurts et al. 2009; Goldberg et al. 2005; Minshew et al. 1997; Ozonoff et al. 1991; Rinehart et al. 2001, 2002; Van Eylen et al. 2011). Inconsistencies between these studies may reflect a number of important issues. For example, variability in task characteristics may impact the ability to detect set shifting performance differences. Aspects of testing such as task complexity and computer versus examiner test administration have been shown to affect the performance of individuals with ASD (Ozonoff 1995). In addition, assessments have frequently been reported on inadequate sample sizes to make allowance for behavioral and cognitive heterogeneity. Comparisons also often include individuals with widely variable intellectual abilities and diverse psychopharmacological histories, and testing is reported on children at various stages of cognitive development.

Understanding the neurocognitive bases of RRBs in ASD involves careful delineation of the types of errors that individuals make during set shifting tasks. Many studies using traditional tests of set shifting have examined perseverative errors in which participants continue to select a response choice that is no longer reinforced. Ragozzino (2007) and others (Gastambide et al. 2012; Kim and Ragozzino 2005) have proposed that set shifting errors can be more precisely differentiated between (1) perseverative responses in which participants fail to shift to a new response after receiving feedback that the correct stimulus response has changed, and (2) regressive errors in which individuals identify the newly-reinforced response choice, but then are unable to maintain this new response set and instead revert back to previously-reinforced choices. Importantly, evidence from human and rodent studies suggests a distinction between the dorsal striatal circuits that support maintenance of a new set following a shift in response set (Brown et al. 2010; Floresco et al. 2006; Shafritz

et al. 2008) and ventral striatal circuits that support initial set shifting (Bissonette et al. 2008; D'Cruz et al. 2011; Ranier 2007). These neurobiological findings suggest that specification of the set shifting error patterns made by individuals with ASD may advance understanding of the neurocognitive and neural system mechanisms contributing to RRBs.

Using a probabilistic reversal learning task in which participants received positive reinforcement on 80 % of correct trials, we previously showed that individuals with ASD make more regressive but not perseverative errors than typically-developing controls, particularly on the 20 % of trials when they are provided with unpredicted, non-reinforcement following a correct response (D'Cruz et al. 2013). These findings suggest that individuals with ASD have difficulty maintaining a new behavioral response set, but it remains unclear whether this is due to a persistence of a previously learned response choice or an inability to maintain new choice patterns during unpredicted, non-reinforcement reflecting a greater dependence on immediate positive reinforcement.

In the present study, we addressed multiple issues in the literature on cognitive flexibility in ASD using a computer-administered test of set shifting ability, the Penn Conditional Exclusion Test (PCET; Kurtz et al. 2004). The PCET is similar to the traditional Wisconsin Card Sorting Test (WCST; Grant and Berg 1948), which Kaland et al. (2008) and others have previously used to demonstrate impaired set maintenance in individuals with ASD. The PCET is a computer-based task, which helps reduce confounding effects of an examiner administration that may selectively impact performance in ASD (Ozonoff 1995; South et al. 2007). Further, we separated regressive and perseverative errors to determine the neurocognitive processes that disrupt set shifting performance in ASD.

This study builds on our previous report of increased rates of regressive errors in ASD during a probabilistic reversal learning task, and extends these findings in three important ways. First, the PCET assesses shifts between response categories involving higher-order cognitive processes that are more supported by prefrontal and association cortices than behavioral response shifting (D'Cruz et al. 2011; Ragozzino 2007). Second, accurate reinforcement contingencies are provided on 100 % of trials. Therefore, we were able to determine whether increased rates of regressive errors in ASD are evident even after a correct response is rewarded, as opposed to being primarily driven by misleading feedback contingencies as in the case of a probabilistic learning test. Third, the PCET provides participants with four possible response choices, rather than the two choices presented in our prior study. This allowed us to differentiate regressive errors back to the previously-reinforced response choices from errors to never-reinforced stimulus items. We predicted that individuals with ASD would show increased rates of regressive errors to previously-reinforced response choices, but not perseverative errors. We also hypothesized that the rate of regressive errors in ASD would be associated with increased severity of RRBs.

Methods

Participants

We examined 60 participants with ASD (50 males) and 55 typically-developing controls (41 males) who were matched on age (ASD range 6–44 years; control range 6–38 years),

gender, and nonverbal IQ (NVIQ) (Table 1; also see Supplementary Table 1 for data on the distributions of gender and IQ across different age strata). For IQ testing, participants 18 years of age and younger completed the Differential Ability Scales-2nd edition (DAS-II; Elliot 2007) (ASD = 37; Control = 31) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999) (ASD = 9; Control = 9), and participants over 18 years of age completed the WASI (ASD = 14, Control = 15). While verbal IQ (VIQ) has been previously shown to be associated with executive function impairments in ASD (Bishop and Norbury 2005; Liss et al. 2001; Pellicano 2007), we matched groups on NVIQ because the PCET places limited verbal demands on participants. Further, many individuals with ASD have more severe deficits in verbal compared to nonverbal IQ, suggesting that matching individuals with ASD and typically developing controls on verbal IQ may result in an ASD sample that is less representative of the broader population (Munson et al. 2008). All participants had full-scale IQ (FSIQ) scores ≥ 70 and NVIQ, VIQ and FSIQ scores all were in the average range for both participant groups (Table 1).

Individuals with ASD were recruited through local autism clinics and community advertisements. Diagnoses of ASD were established with the Autism Diagnostic Inventory-Revised (ADI; LeCouteur et al. 1989) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1989), and were confirmed by expert clinical opinion and based on DSM-IV criteria (APA 2000). Participants with ASD were excluded if they had a known genetic or metabolic disorder associated with ASD (e.g., Fragile $\times$ syndrome, tuberous sclerosis) or were currently taking medications known to affect cognitive performance, including antipsychotic, psychostimulant, antidepressant, or anticonvulsant drugs. Two participants included in the present study met classification criteria for autism on the ADI and were identified as having ASD based on clinical expertise, but they were unavailable for ADOS testing. These participants were included in final analyses; results were substantively identical when analyses were performed without these individuals. Adult participants provided written informed consent, and participants under 18 provided assent along with a parent's written consent. All procedures were approved by the local Institutional Review Board.

Typically developing participants were recruited through local advertisements. Potential control participants were asked about their family medical history prior to study enrollment as we have done previously (Mosconi et al. 2013; Takarae et al. 2004, 2007). They reported no history of psychiatric or neurological disorders, family history of ASD in first or second-degree relatives, or a history in first-degree relatives of a developmental or learning disorder, psychosis, or obsessive-compulsive disorder. Controls were excluded if they scored ≤ 8 on the Social Communication Questionnaire (SCQ; Rutter et al. 2003). We selected a more conservative cutoff than is suggested by the test authors to determine control eligibility (ASD cutoff = 15) because we have previously found across a series of studies that some controls with scores ≤ 8 may show subtle phenotypic features associated with ASD.

Procedures

The Penn Conditional Exclusion Test (PCET; Kurtz et al. 2004) was administered to participants while they were seated comfortably in front a touchscreen computer (Fig. 1).

PCET stimuli included a series of 4 similar objects positioned in a horizontal row. Three of the objects were matched according to a computer-determined sorting principle (shape, size, or line thickness), but participants were not informed of the correct sorting principle. They were instructed to select the item that did not belong with the others. Participants were therefore required to learn and apply a cognitive rule using computer feedback written on the computer screen immediately after each response (“Correct” or “Wrong”). After participants correctly identified the object that did not conform to the sorting principle for ten consecutive trials, the sorting principle shifted without warning, requiring participants to select objects based on a new sorting rule. Participants were required to select a response in order to advance to the next trial, and the task was self-paced.

Three sorting principles, or categories, were presented to all participants unless they failed to complete the first category within 48 trials. Testing was discontinued if participants failed Category 1 because they had not learned a rule from which a set switch could be evaluated. A total of nine individuals with ASD and three controls failed to complete the first category (see Supplementary Materials Table 2 for demographic characteristics of participants who failed Category 1). Participants who failed Category 1 had lower FSIQ, $t(113) = 2.46$, $p = 0.02$, $M_{Diff} = 11.54$, $SE = 4.69$, and NVIQ, $t(109) = 2.74$, $p = 0.01$, $M_{Diff} = 12.15$, $SE = 4.43$, scores than those who successfully completed the category. Across both the ASD and control groups, participants who failed Category 1 did not differ from those who completed Category 1 on gender, *Mann–Whitney U*(113) = 589.50, $z = -3.33$, $p = 0.71$, age, $t(113) = 1.53$, $p = 0.13$, or VIQ, $t(109) = 1.42$, $p = 0.16$. The remaining 51 individuals with ASD and 52 controls received Categories 2 and 3, based on the assumption that successful completion of Category 1 indicated a general ability to perform the test. However, some participants failed these later categories. Criteria for failure of Category 2 and 3 was identical to that of Category 1, namely, failing to complete ten consecutive correct responses within 48 trials. No time-based criteria were used to determine category failure, and criteria were the same for all participants regardless of age.

Incorrect responses in Category 1 *prior* to the first correct response were counted as *never-reinforced general errors*. Incorrect responses in Category 1 that occurred after the first correct response were counted as *set maintenance errors*. In Categories 2 and 3 we had particular interest in two specific error types, *perseverative errors* and *regressive errors*.

Perseverative errors indicate persistent use of an incorrect strategy in the face of negative feedback after a rule change, suggesting an inability to switch to a new response set. Perseverative errors were responses in which participants continued to follow the previously-reinforced rule following negative feedback but *prior* to the first correct response to the new rule. Regressive errors were responses in which participants sorted according to the previously-reinforced rule *after* the first correct response choice in a new category, thus representing a failure to maintain a new response set in favor of a previously-reinforced one. This differentiation of perseverative and regressive errors is most clear in Category 2, where there was one previously learned rule and one new correct rule. However, we also examined these error types in Category 3, where we differentiated between regressive errors resulting from use of the correct rules from Category 1 and those resulting from use of the correct rule from Category 2. In doing so, we aimed to determine whether there was a more robust

tendency of individuals with ASD to regress to the initially reinforced or the most recently reinforced rule.

Errors in Category 2 that could not be considered regressive or perseverative were considered *never-reinforced*. Never-reinforced general errors occurred when a participant chose an incorrect response in Category 2 that did not conform to the previously-reinforced Category 1 rule. Errors in Category 3 that could not be considered regressive or perseverative were considered *previously-reinforced general errors*. Previously-reinforced general errors occurred when a participant used a Category 1 rule to respond in Category 3 *prior* to the correct use of the Category 3 rule. These errors reflected a tendency to persevere on previously-reinforced response patterns, but were different from perseverative errors in that they were not based on the rule that was most recently reinforced. They were different from regressive errors to Category 1 in that they occurred prior to initial acquisition of the new, correct response set. Each participant's total number of errors did not include their response to the first trial after a rule change. A sample response pattern is provided in Supplementary Materials Table 3 to illustrate each of the possible error types.

All 3 categories of the PCET included a small minority of “ambiguous trials” in which the stimulus that was selected could have been selected based on multiple sorting principles (see Supplementary Materials Table 3 for sample *ambiguous trials*). For these trials, a step-down procedure was used to determine how to score the trial. First, ambiguous trials in which the participant chose an item that conformed to both the correct and incorrect sorting principle were counted as correct. Second, if one of the possible sorting principles qualified the response as either a regressive or a perseverative error, and both the preceding and the subsequent trial were also of the same error type, then the response was considered an error of the same type as those preceding and following it. Third, if the trial could not be considered either a regressive or perseverative error because the preceding or subsequent trials were not of the same error type, because neither sorting principle was previously reinforced as in the case of Category 1 trials, or because the correct sorting rule had not yet been used, then the response was considered either a never-reinforced or a previously-reinforced general error depending on the error type. Fourth, if the two sorting principles equated to a previously-reinforced general error and a never-reinforced general error, then the determination was based on whether the preceding and subsequent trials were consistent with one of these error classifications, or if a pattern could not be established, the error was labeled as previously-reinforced general error. In Category 3, errors in which participants were not responding to any discernable rule set (e.g., selecting the second stimulus from the left in Fig. 1) were classified as never-reinforced general errors.

Measures of Restricted and Repetitive Behaviors

Measures of RRBs were derived from the ADOS and the ADI. The RRB subscale of the ADOS uses clinician ratings to assess unusual sensory interests, atypical motor mannerisms, restricted interest in specific topics or objects, repetitive behaviors, and compulsions or rituals. We computed this subscale score using an algorithm corresponding to the second edition of the ADOS (Lord et al. 2012). We also examined the RRB algorithm score of the ADI. To further differentiate the types of RRBs that were associated with deficits in set

shifting, we analyzed two distinct types of RRBs based on prior factor analyses: an *insistence on sameness* factor (IS) that included items related to individuals' difficulty with changes in their routine or environment, and a *repetitive sensory-motor actions* factor (RSMA) related to individuals' repetitive motor behaviors or unusual sensory interests (Cuccaro et al. 2003; Mooney et al. 2009). We predicted that increased rates of regressive errors for individuals with ASD would be associated with more severe RRBs on the ADOS and ADI, but not with Social or Communication abnormalities. We also hypothesized that increased rates of set shifting errors would be selectively related to increased IS severity, but not severity of RSMA.

Statistical Analyses

We used a series of 2×2 ANOVAs to examine the effects of diagnostic group (ASD vs. control) and category number (2 or 3) on performance accuracy and the rate of different error types following a set shift (perseverative, regressive, previously-reinforced general, and never-reinforced general). An additional 2×2 ANOVA was used to examine the effect of diagnostic group (ASD vs. control) and category rule used (1 or 2) on the rate of regressive errors in Category 3. For all error types that were significantly different between individuals with ASD and controls, we examined the relationships between error rates and age, IQ and clinical ratings of RRBs.

Results

PCET Performance

When only participants who completed Category 1 were examined, individuals with ASD committed significantly more errors across all categories ($M = 10.90$, $SD = 6.43$) than controls ($M = 8.03$, $SD = 6.43$), $F(1, 101) = 5.13$, $p = 0.03$, $\eta_p^2 = 0.05$. Group differences in total errors did not vary as a function of category, $F(2, 202) = 0.99$, $p = 0.37$. During Category 1, individuals with ASD committed a greater number of never-reinforced general errors, $t(102.72) = 2.14$, $p = 0.04$, $M_{Diff} = 3.61$, $SE = 1.69$, and set maintenance errors, $t(92.64) = 2.48$, $p = 0.02$, $M_{Diff} = 3.73$, $SE = 1.50$, compared to controls. However, the difference in set maintenance errors was not significant when participants who failed to complete Category 1 were excluded, $t(90.69) = 1.77$, $p = 0.08$, $M_{Diff} = 1.28$, $SE = 0.72$. There was no group difference in the number of categories completed when excluding the 12 participants who failed to complete Category 1, $t(97.10) = 1.73$, $p = 0.09$, $M_{Diff} = 0.20$, $SE = 0.12$. The remaining analyses do not include participants who failed to complete Category 1. Group means and standard deviations for each PCET error type and category are presented in Table 2. Successful completion of Category 1 indicated that the individual was generally able to understand and correctly perform the task, and therefore these participants received Categories 2 and 3. However, 18 individuals with ASD and 5 typically-developing controls failed Category 2 after successfully completing Category 1, and 25 individuals with ASD and 16 typically-developing controls failed Category 3, suggesting that test difficulty increased as more sorting rules were reinforced. Individuals with ASD who completed Category 1 made more total errors across Categories 2 and 3 ($M = 28.61$, $SD = 18.61$) than typically-developing controls ($M = 21.06$, $SD = 14.64$), $F(1, 101) = 5.24$, $p = 0.02$, $\eta_p^2 = 0.05$.

The magnitude of increased total error rates in ASD did not vary as a function of Category when Categories 2 and 3 were compared, $F(1, 101) = 0.11, p = 0.74$. Consistent with our hypothesis, individuals with ASD made more regressive errors ($M = 11.29, SD = 12.24$) relative to controls ($M = 6.25, SD = 9.92$), $F(1, 101) = 5.29, p = 0.02, \eta_p^2 = 0.05$ (Fig. 2). Further analysis of Category 3 regressive errors, in which we separated errors by whether participants used the Category 1 versus Category 2 rule did not reveal group differences as a function of rule choice, $F(1, 101) = 5.10, p = 0.39$. There was no group difference in the number of perseverative errors collapsed across Categories 2 and 3, $F(1, 101) = 0.00, p = 0.99$ (Fig. 2), and the Group $\times$ Category interaction was not significant, $F(1, 101) = 0.48, p = 0.49$.

Individuals with ASD made more never-reinforced general errors ($M = 8.94, SD = 11.60$) relative to controls ($M = 4.75, SD = 5.64$), $F(1, 101) = 5.47, p = 0.02, \eta_p^2 = 0.05$. The magnitude of increased never-reinforced general error rates in ASD did not vary as a function of Category when Categories 2 and 3 were compared, $F(1, 101) = 1.65, p = 0.20$.

Clinical Correlations

Next, we examined the relationship between ADOS and ADI ratings of RRB and PCET performance deficits in individuals with ASD, specifically increased rates of total errors, regressive errors, and never-reinforced general errors. For participants with ASD who completed Categories 2 and 3, more abnormal ADOS RRB scores were associated with higher total error rates across the entire test ($r = 0.31, p = 0.03$) and with more regressive errors in Category 2 ($r = 0.31, p = 0.03$), but not in Category 3 ($r = 0.07, p = 0.65$). Regressive error rates were not associated with ADI RRB scores. However, when we examined the relationship between regressive errors and IS and RSMA separately, Category 3 regressive errors to Category 1 rules were significantly associated with more severe IS ($r = 0.33, p = 0.03$) but not RSMA clinical ratings ($r = 0.04, p = 0.77$). Regressive errors to Category 2 were not associated with either IS or RSMA ratings ($r_s = 0.02, 0.11, p_s = 0.91, 0.45$).

Increased rates of never-reinforced general errors in Category 2, which reflect difficulty identifying the new sorting principle after a category shift, were associated with more severe IS ($r = 0.31, p = 0.03$) on the ADI, but not with RSMA ratings ($r = 0.12, p = 0.43$). PCET performance was selectively associated with more severe RRBs and was not associated with clinical ratings of social or communication abnormalities from the ADOS or ADI ($p_s > 0.05$).

We also assessed the effects of IQ on PCET performance. For the ASD group, increased FSIQ ($r = -0.33, p = 0.02$) and NVIQ ($r = -0.37, p = 0.01$) each were associated with fewer total errors across the PCET. Increased VIQ was related to fewer perseverative errors for individuals with ASD as well ($r = -0.35, p = 0.01$). No other relationships between IQ measures and PCET performance were significant for the ASD or control groups (see Supplementary Table 4 for correlations).

Despite studying a large age range, few relationships were seen between participants' age and PCET performance. Older individuals with ASD made fewer total errors than younger individuals with ASD ($r = -0.31$, $p = 0.03$). For controls, increased age was positively associated with category completion ($r = 0.20$, $p = 0.03$) and negatively associated with never-reinforced general errors ($r = -0.22$, $p = 0.02$). No other age-related effects on PCET performance were found in either the ASD or control group.

Discussion

Here, we demonstrate that while individuals with ASD are able to learn a new cognitive rule to guide responses, they show difficulty maintaining this new rule and instead regress to using previously-reinforced cognitive strategies. Difficulty maintaining new response preferences in lieu of old ones was related to clinically rated severity of RRBs in individuals with ASD, and specifically an increased need for sameness rather than repetitive sensorimotor behaviors. Importantly, deficits in set shifting were uniquely associated with RRBs, and they were not related to social or communication deficits.

We previously reported increased rates of regressive errors in ASD during a probabilistic reversal learning test (D'Cruz et al. 2013), and the present study extends this work in three important ways. First, while our previous study used a simple test of spatial discrimination, this study explores more challenging cognitive set shifts requiring individuals to deduce a guiding principle upon which to differentiate items. During this test, individuals choose objects based on an undisclosed sorting rule, which requires a higher level of cognitive rule maintenance and modification than assessed in our prior study. The present results thus provide novel evidence that individuals with ASD exhibit a clinically relevant difficulty maintaining new choice patterns in lieu of previous ones for cognitive rules, as well as rules for simple behavioral response choices. Second, by using a four-choice test, rather than a two-choice test as in our prior study, we were able to demonstrate that individuals with ASD fail to maintain a newly identified response pattern and they regress preferentially to previously-reinforced response choices rather than to choices that have not been previously-reinforced. Last, while our prior study of probabilistic reversal learning demonstrated that individuals with ASD make regressive errors more frequently than controls when they receive negative feedback, we find here that they regress even in the context of continuous positive feedback. Therefore, increased rates of regressive errors in ASD are due to a failure to maintain set rather than a heightened sensitivity to the intermittent removal of reward.

Prior studies of cognitive flexibility in individuals with ASD have typically focused on overall accuracy in set shifting without analyzing the types of errors underlying performance deficits. For example, Kaland et al. (2008) reported elevated rates of perseverative, non-perseverative, and "failure to maintain set" errors on the WCST in ASD. However, the WCST uses a definition of perseverative errors that encompasses both perseverative and regressive errors as defined here, which may not fully capture specific cognitive impairments in clinical populations (Barceló and Knight 2002; Heaton et al. 1993). Furthermore, "failure to maintain set" errors, as calculated in the WCST, have been referred to as "random errors" that represent distractibility rather than cognitive flexibility (Barceló and Knight 2002; Figueroa and Youmans 2013). We were able to distinguish a specific

pattern of neurocognitive deficit in which individuals with ASD are not able to maintain newly acquired rules and specifically revert back to previously-reinforced response patterns. By analyzing different types of errors, we believe these findings may help explain some of the inconsistencies across previous studies of cognitive flexibility in ASD (Ozonoff et al. 2004, Van Eylen et al. 2011). Notably, individuals with ASD who were able to successfully learn and apply new cognitive rules, as shown by completion of Category 1, still experienced difficulty consistently maintaining a new response set. They reverted to previously-reinforced response patterns, but they did not demonstrate an increased rate of perseverative errors, suggesting that they could successfully modify a cognitive rule in response to shifting reinforcement conditions. Thus, the set-shifting deficit demonstrated here was specific to maintaining a new correct response relative to previously preferred response choices. By examining a larger sample, and restricting our analyses to only those individuals with ASD who could learn the basic sorting rule, we find a selective impairment in maintaining newly-reinforced response patterns. It should be noted that a small subgroup of individuals with ASD failed to complete Category 1 and thus appear to show deficits in rule learning (Solomon et al. 2011). More systematic analyses of initial rule learning in ASD are needed to determine if these individuals represent a distinct subgroup of individuals with ASD.

Our findings also suggest that failures to maintain new cognitive rules because of an enhanced preference for previously-reinforced cognitive rules may contribute to repetitive patterns of behavior in ASD. This neurocognitive deficit appears to be one mechanism selectively underlying the strong need for sameness in routine and in the environment shown by many individuals with ASD. This deficit also may, in turn, result in a high rate of regression to previous patterns of behavior or reasoning, even for those individuals who are capable of learning and using new rules to intermittently guide responding. Importantly, we find that this neurocognitive deficit is specifically related to RRBs and the need for sameness, and not with social or communication abnormalities in ASD.

The observation that individuals with ASD exhibit an increase in regressive errors may also be informative for understanding the neural substrates underlying cognitive inflexibility, and putatively, RRBs. Preclinical studies offer evidence for a dissociation between the neural circuits supporting perseverative and regressive errors (Dias et al. 1997; McAlonan and Brown 2003; Ragozzino et al. 1999). The pattern of results observed in the present study indicates that individuals with ASD who could successfully perform this task were able to recruit prefrontal cortical circuits to form new response sets (e.g., Kim and Ragozzino 2005; Ranier 2007), but that a breakdown occurs either in the striatum or in the neural pathways connecting frontal cortices and striatum (e.g., Ragozzino et al. 2002; Ragozzino and Choi 2004). The increased rate of regressive errors observed in our study suggests that dysfunction of medial striatal and prefrontal cortical systems supporting stable behavioral plans interferes with the ability to maintain newly-reinforced response sets (Floresco et al. 2006). While these results selectively implicate frontostriatal circuits in ASD, in vivo studies of brain function during set shifting in ASD are needed. Prior findings suggest structural abnormalities in the basal ganglia and prefrontal cortices in ASD (Cody et al. 2002; Cody-Hazlett et al. 2006; Sears et al. 1999) and indicate that caudate overgrowth is associated with increased rates of perseverative errors on the WCST (Voelbel et al. 2006). Functional

neuroimaging studies also have documented atypical activation of frontostriatal systems during tests of cognitive flexibility and executive control (Agam et al. 2010; Deshpande et al. 2013; Kenet et al. 2012; Langen et al. 2012; McAlonan et al. 2005; Rinehart et al. 2002; Takarae et al. 2007).

GABAergic and serotonergic drug effects in frontal cortex and medial striatum facilitate set shifting and reversal learning by selectively decreasing regressive errors in mice (Brown et al. 2012; Kim and Ragozzino 2005; Palencia and Ragozzino 2004; Ragozzino et al. 2002; Ragozzino and Choi 2004). GABAergic and serotonergic alternations might contribute to the set shifting deficits we observed in ASD, and might represent useful target systems for drug development and treatment aimed at reducing RRBs (Langen et al. 2012; McAlonan et al. 2005; Rinehart et al. 2002). Indeed, serotonergic drugs frequently are used to target RRBs in ASD (Veenstra-VanderWeele and Blakely 2011), and preclinical studies have identified multiple 5HT receptor subtypes critically involved in cognitive flexibility in mice (Amodeo et al. 2014; Brown et al. 2012; Baker et al. 2011; Mohler et al. 2012).

We included participants from a wide age range for multiple reasons. First, this allowed us to examine developmental effects, at least in a preliminary way. Age effects on PCET performance were modest for the age range studied here, and similar in individuals with ASD and controls. It is possible that maturation of set shifting abilities occurs earlier than the ages examined here. Alternatively, cross-sectional designs may not be sufficient for detecting age-related improvements in cognitive flexibility in childhood and adolescence, or in detecting alterations in developmental trajectories in ASD as suggested previously (Pellicano 2010). Second, by examining a large age range we were able to study a large sample of medication-free individuals with ASD. Despite including only individuals with ASD who were unmedicated and thus may have shown less severe RRBs relative to those on medication, we found significant increases in the rate of set shifting errors in ASD. A broader sample including both medicated and non-medicated individuals may be required to clarify the magnitude of the relationship between RRBs and set shifting across a wide range of symptom severity.

We used two different measures of IQ (DAS-II, WASI) so that individuals could be tested across a wide age range, and the majority of individuals could be tested using the DAS-II which has fewer verbal demands than many other commonly used IQ measures for children. Thus, the DAS-II may have advantages for testing cognitive abilities in children with ASD who may show reduced ability understanding verbal instructions. Still, our analyses of the relationships between IQ and PCET performance should be interpreted with caution given the additional variability that the use of two distinct IQ measures may have contributed to our estimates.

We conclude that RRBs do not just reflect atypical preferences as may be seen clinically, or general behavioral rigidity, but instead appear to reflect a specific difficulty with cognitive and behavioral set maintenance. Importantly, when excluding the 12 participants who failed to complete Category 1 (including 9 individuals with ASD and 3 controls), individuals with ASD did not differ from controls in the number of categories completed. This finding is consistent with previous work demonstrating that individuals with ASD do not differ from

controls in their ability to complete a set-shifting task, despite key increases in error commission rates and thus the number of trials it takes them to complete a set (Goldberg et al. 2005; Landa and Goldberg 2005; Solomon et al. 2011; Yerys et al. 2009). Specifically, individuals with ASD experience difficulty maintaining new rules to guide responding. Even when they successfully identify and use a new rule, they tend to revert back to previously learned response preferences. Findings from the present study demonstrate that individuals with ASD have specific differences in the cognitive processes that support set maintenance, and these differences likely produce the performance differences observed on set shifting tasks. These processing differences implicate frontostriatal systems that could be targeted by new cognitive or pharmacological treatments. Such approaches are needed to reduce the severity of RRBs and the significant burden they confer on individuals with ASD and their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Sample trial of the PCET

Fig. 2.
Number of regressive and perseverative errors collapsed across Categories 2 and 3 for individuals with ASD and typically-developing controls

Table 1

Demographic and clinical characteristics

	ASD Mean (SD)	Control Mean (SD)	t(df)
Age	15.1 (8.02)	15.9 (7.5)	0.60 (113)
FSIQ	100.1 (17.2)	108.9 (12.6)	3.15 (113)*
VIQ	100.1 (17.9)	110.2 (15.1)	3.19 (109)*
NVIQ	101.1 (17.2)	106.6 (11.5)	1.96 (109)
ADI IS	0.33 (0.21)		
ADI RSMA	0.31 (0.17)		
ADI (Diag.) RRB subscale	5.87 (2.24)		
ADI (Curr.) RRB subscale	4.44 (2.39)		
ADOS-2 RRB subscale	2.63 (1.90)		

RBS-R Repetitive Behaviors Scale-Revised, *ADI-R* Autism Diagnostic Interview-Revised, *IS* Insistence on Sameness, *RSMA* Repetitive Sensory-Motor Actions, *RRB* Restricted and Repetitive Behaviors, *ADOS* Autism Diagnostic Observation Schedule, *Diag* diagnostic algorithm based on ratings of symptom severity at ages 4–5 years, *Curr* current behavior algorithm based on ratings of symptom severity in the past 3 months

* Group differences significant at $p < .05$

Table 2

PCET errors for participants with ASDs and typically-developing controls

	Error type	ASD ^a Mean (SD)	Control ^b Mean (SD)
Category 1	General (<i>never-reinforced</i>)	7.85 (10.78)	4.24 (7.08)
Category 1	Set maintenance *	2.41 (4.20)	1.13 (3.02)
Category 2	General (<i>never-reinforced</i>) *	3.53 (6.27)	1.13 (1.92)
	Perseverative	3.39 (4.91)	2.96 (3.09)
	Regressive	3.53 (5.55)	2.00 (3.06)
Category 3	General (<i>never-reinforced</i>)	1.33 (2.82)	.60 (1.33)
	General (<i>previously-reinforced</i>)	3.82 (5.04)	4.48 (4.72)
	Perseverative	5.20 (6.26)	5.63 (6.53)
	Regressive *	7.59 (9.64)	4.25 (8.05)
	Regressive to Category 1 rule	3.78 (5.17)	2.52 (5.11)
	Regressive to Category 2 rule	3.37 (4.72)	1.60 (3.33)

PCET Penn Conditional Exclusion Test. Category 1 means presented in this table include the nine individuals with ASD and 3 controls who failed to complete Category 1. In Category 3, regressive errors to items that conformed to both Category 1 and Category 2 sorting principles are not displayed in this table, but were included in the calculation of total regressive errors for Category 3

* Group differences significant at $p < .05$

^aCategory 1 (n = 60), Category 2 and 3 (n = 51)

^bCategory 1 (n = 55), Category 2 and 3 (n = 52)