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Neural correlates of set-shifting in children with autism

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Abstract

Autism spectrum disorder (ASD) is often associated with high levels of inflexible thinking and rigid behavior. The neural correlates of these behaviors have been investigated in adults and older adolescents, but not children. Prior studies utilized set-shifting tasks that engaged multiple levels of shifting, and depended on learning abstract rules and establishing a strong prepotent bias. These additional demands complicate simple interpretations of the results. We used functional magnetic resonance imaging (fMRI) to investigate the neural correlates of set-shifting in 20 children (ages 7–14) with ASD and 19 typically developing, matched, control children. Participants completed a set-shifting task that minimized non-shifting task demands through the use of concrete instructions that provide spatial mapping of stimuli-responses. The shift/stay sets were given an equal number of trials to limit the prepotent bias. Both groups showed an equivalent ‘switch cost’, responding less accurately and slower to Switch stimuli than Stay stimuli, although the ASD group was less accurate overall. Both groups showed activation in prefrontal, striatal, parietal, and cerebellum regions known to govern effective set-shifts. Compared to controls, children with ASD demonstrated decreased activation of the right middle temporal gyrus across all trials, but

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increased activation in the mid-dorsal cingulate cortex/superior frontal gyrus, left middle frontal and right inferior frontal gyri during the Switch vs. Stay contrast. The successful *behavioral* switching performance of children with ASD comes at the cost of requiring greater engagement of frontal regions, suggesting less efficiency at this lowest level of shifting.

Keywords

autism; cognitive control; set-shifting; fMRI; cingulate; prefrontal cortex

Individuals with autism spectrum disorders (ASD) demonstrate rigid, inflexible cognitions and behavior (Geurts, Corbett, & Solomon, 2009). These behaviors occur in response to changes in their daily routine/environment, and in their approach to problem solving. Parents report observing these behaviors in everyday settings (Gioia, Isquith, Kenworthy, & Barton, 2002; Kenworthy et al., 2005; Rosenthal et al., 2013; Smithson et al., 2013). In the lab, we capture cognitive components of these behaviors with set-shifting tasks that require individuals to infer (or follow) rules, like sorting pictures by shape, and then *shift* to a new set of rules. Regardless of cognitive functioning, children and adults with ASD demonstrate significant impairments compared to controls using various forms of card sorting tasks (Faja & Dawson, 2013; Geurts et al., 2009; Reed, Watts, & Truzoli, 2011; Rumsey, 1985; Zelazo, Jacques, Burack, & Frye, 2002), reversal learning tasks (D'Cruz et al., 2013; Hughes, Russell, & Robbins, 1994; Ozonoff et al., 2004; Yerys, Wallace, et al., 2009), and other open-ended or semi-directed set-shifting tasks (Solomon, Ozonoff, Cummings, & Carter, 2008; Yerys, Wolff, Moody, Pennington, & Hepburn, 2012).

Set-shifting develops dramatically across childhood, as children progress from following single rules to shifting between two competing sets of rules about a single stimulus (Bunge & Zelazo, 2006; Cepeda, Kramer, & Gonzalez de Sather, 2001; Cepeda & Munakata, 2007; Chatham, Yerys, & Munakata, 2012; Crone, Bunge, van der Molen, & Ridderinkhof, 2006; Crone, Donohue, Honomichl, Wendelken, & Bunge, 2006; Davidson, Amso, Anderson, & Diamond, 2006; Zelazo et al., 2003; Zelazo, Reznick, & Spinazzola, 1998). Successful set-shifting and other executive function performance correlates with adaptive and academic functioning in typical development and in children with ASD (Clark, Prior, & Kinsella, 2002; Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002; Lopata et al., 2012; Pugliese et al., 2014), while set-shifting deficits are associated with maladaptive behaviors that are characteristic of ASD (D'Cruz et al., 2013; Lopez, Lincoln, Ozonoff, & Lai, 2005; Reed et al., 2011; Yerys, Wallace, et al., 2009). The biological mechanisms of rigid, inflexible cognitions and behaviors are relatively understudied in ASD, and there is also a need for better decomposition of set-shifting impairments (Geurts et al., 2009).

Accurate measurement of set-shifting depends on accurate decomposition of the construct and its neural correlates. Many behavioral studies in ASD have used classic neuropsychological tasks such as the Wisconsin Card Sorting Task (Hill, 2004; Kenworthy, Yerys, Anthony, & Wallace, 2008; Pennington & Ozonoff, 1996; Russo et al., 2007; Sergeant, Geurts, & Oosterlaan, 2002), but these complex tasks limit the ability to attribute poor performance to a specific level of set-shifting. Furthermore, non-shifting executive

components (e.g., strong prepotent bias, verbal working memory for abstract rules) can also play a role in poor performance. These factors limit insight into the source of the deficit observed in ASD. We adopt a well-articulated model of set-shifting that poses four levels of increasing complexity (Bunge & Zelazo, 2006): response reconfiguration, attention, stimulus appraisal, and task. Response reconfiguration is reversing previously rewarded stimulus-response maps. Attention shifts require switching a response between *two distinct stimuli*, 'A' vs. 'B', without changing response mappings. Bunge and Zelazo (2006) referred to this as flexible rule use with 'univalent' stimuli. These lowest levels of set-shifting have been explored in adults (Rushworth, Passingham, & Nobre, 2002, 2005) and in typically developing children (Crone, Bunge, et al., 2006; Crone, Donohue, et al., 2006). Stimulus appraisal requires switching between *two features within a single stimulus* like shape and color, and is prominent in common neuropsychological measures used in ASD research (e.g., Wisconsin Card Sorting Task, intradimensional/extradimensional shift task, and Dimensional Change Card Sort; Hill, 2004; Kenworthy et al., 2008; Pennington & Ozonoff, 1996; Russo et al., 2007; Sergeant et al., 2002). Bunge and Zelazo (2006) referred to this as flexible rule use with 'bivalent' stimuli. Task shifting requires switching between two unrelated tasks, or flexible use of 'higher-order' rules to switch between task sets (Bunge & Zelazo, 2006).

Brain imaging studies in the normative population point to the importance of activation in executive circuitry for all set-shifting levels, such as lateral prefrontal and superior medial prefrontal, cingulate, striatum, parietal, and cerebellum regions (Buchsbaum, Greer, Chang, & Berman, 2005; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Crone, Donohue, et al., 2006; Ezekiel, Bosma, & Morton, 2012; Morton, Bosma, & Ansari, 2009; Shafritz, Kartheiser, & Belger, 2005; Smith, Taylor, Brammer, & Rubia, 2004; Wager, Jonides, & Reading, 2004; Solomon et al., 2009; Shafritz, Dichter, Baranek, & Belger, 2008; Schmitz et al., 2006; Wendelken, Munakata, Baym, Souza, & Bunge, 2012; Rubia et al., 2006). Developmental studies demonstrate that younger school age children show greater prefrontal cortex activation (lateral prefrontal, cingulate), and decreased parietal and striatal activation in comparison to older children and young adults (Crone, Donohue, et al., 2006; Morton et al., 2009; Wendelken et al., 2012; but see Rubia et al., 2006). These changes in functional activation in prefrontal and parietal cortices converge with known developmental changes in both gray and white matter (Lenroot et al., 2007; Lenroot & Giedd, 2006) in these same regions. This recent functional neuroimaging evidence converges with long standing neuropsychological studies showing impaired set-shifting performance on the Wisconsin Card Sorting Task (Milner, 1963) and perseverative, environmentally dependent behavior (Lhermitte, 1986) in patients with frontal lobe lesions.

The existing functional neuroimaging set-shifting studies in ASD focus on adults and adolescents. They also combine multiple shifting and non-shifting executive demands. Individuals with ASD demonstrate decreased activation compared to typically developing controls in lateral prefrontal, mid-dorsal anterior cingulate cortex (mdACC), striatum, parietal, cerebellum, and temporal regions in the preparing-to-overcome-prepotency task (Solomon et al., 2009) and on an oddball switching task (Shafritz et al., 2008), which combines response reconfiguration, verbal working memory for abstract rules across the

task (e.g., red square means play the opposite game), and a strong prepotent bias for one stimulus-response set. Another study of adults with ASD demonstrated increased bilateral parietal activation in an adapted Meiran spatial switching task, which combined response reconfiguration and stimulus reappraisal (Schmitz et al., 2006). These functional studies implicate an altered frontal-striatum-parietal-cerebellum network for set-shifting, but we lack specificity for whether one or multiple set-shifting levels are altered in ASD. Therefore, the present study targets the lowest level–response reconfiguration–while minimizing other task demands. Moreover, the existing ASD neuroimaging studies do not inform us about shifting in late childhood and early adolescence, which is a key period of brain development (Lenroot et al., 2007; Lenroot & Giedd, 2006), therefore what is observed in adolescence and adulthood may not apply. Thus, the present study provides a novel extension of set-shifting into a younger age group than has been previously investigated.

The present study compares the neural correlates of response reconfiguration shifting in children with ASD (7-14 years) to typically developing control (TDC) children. This study provides a novel paradigm of the lowest set-shifting level by requiring children to reconfigure responses without switching attention, stimulus reappraisal, memorizing abstract rules, or managing a strong prepotent bias to one of the two response sets. In this task, the instruction cues showed children that each stimulus (circle and square) maps onto a response button (right vs. left) based on the spatial location. See Figure 1. Switch and Stay trials were identical in terms of stimuli characteristics. Activation during the initial Switch trials of an epoch (relative to the last Stay trials in an epoch) reflects the initiation of a new behavior response set in the face of an existing competing response set. Response selection in the face of a competing response set is termed a “switch cost”, as it is slower and more-error prone. We minimized other task demands (e.g., stimulus reappraisal, verbal working memory, inhibition) by: having children classify stimuli by the same feature on all trials, providing equal numbers of trials for each response set; and providing concrete visual instructions that only had to be maintained for short blocks (~5 trials). We tested the following behavioral predictions: both groups would respond faster and more accurately to Stay trials than Switch trials; and children with ASD would perform worse on Switch trials than a matched typically developing control (TDC) group. Regarding brain activation during the Switch vs. Stay contrast, we expected activation in the lateral prefrontal cortex, mdACC, striatum, parietal, and cerebellum based on prior set-shifting studies, particularly those focused on response reconfiguration (Rushworth et al., 2002, 2005). Based on the only other ASD study that used a spatial set-shifting task (Schmitz et al., 2006), we expected intact performance and increased activation within the set-shifting network for children with ASD.

Methods and Materials

Participants

Thirty-one children with ASD (without intellectual impairment) and 27 typically developing (TDC) control children were recruited for this study. Twenty-one children were excluded due to: 1) failure to meet diagnostic criteria (ASD n=3; TDC n=1); 2) excessive head motion (root mean square>1.75mm of maximum displacement or .0175 radians of translation; ASD n=6; TDC n=6); 3) declining to complete at least four runs of scanning (ASD n=2); 4)

performance not above chance (TDC $n=1$). We conducted analyses on four runs for six children with ASD: Four had excessive motion and two had chance level performance. Also, one child in the TDC group made a movement $>1.75\text{mm}$ in the second volume of a run and the run was retained after dropping the first four volumes. The sample loss due to motion artifact (ASD=19%; TDC=22%) was expected given the lengthy fMRI procedure (5 runs*3 min 15 seconds=16 minutes 15 seconds) and the lack of stimulant medication in the ASD group; our rates are also in line with prior reported scan success rates for this age and diagnostic group (Byars et al., 2002; Yerys, Jankowski, et al., 2009). The final imaging sample included 39 children (TDC $n=19$; ASD=20). Children were recruited through an outpatient ASD clinic. All children were between 7- and 14-years, and had a Full Scale IQ 80 (Wechsler Intelligence Scale for Children–4th Edition, or Wechsler Abbreviated Scale of Intelligence) (Wechsler, 1999, 2003). Written informed consent and assent were obtained according to Institutional Review Board guidelines.

Children with ASD received an expert clinical diagnosis based on Diagnostic and Statistical Manual of Mental Disorders–*Fourth Edition –Text Revised* criteria (American Psychiatric Association, 2000). They also met the criteria for ‘broad ASD’ based on scores from the Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994) and/or the Autism Diagnostic Observation Schedule (Lord et al., 2000) following criteria established by the Collaborative Programs for Excellence in Autism (Lainhart et al., 2006). Children with ASD were screened through a parent phone interview and excluded if parents reported a history of genetic (e.g., Fragile X), mood, psychotic, or neurological disorders (e.g., seizure disorder), and if they were prescribed atypical antipsychotics. Methylphenidate was withheld at least 24 hours prior to testing ($n=1$), one child was prescribed atomoxetine and another was prescribed topiramate. TDCs were screened and excluded if they or a first-degree relative had developmental, language, learning, neurological, or psychiatric disorders, psychiatric medication usage, or if the child met the clinical criteria for a childhood disorder on the Child Symptom Inventory – Fourth Edition or Child and Adolescent Symptom Inventory (Gadow & Sprafkin, 2000, 2010). The groups were matched on age, cognitive ability, and sex-ratio. See Table 1.

Task Procedure

All stimuli were created in Microsoft Powerpoint and presented in E-prime 2.0 (Psychological Software Tools, Inc., PA), and viewed via a magnet-compatible projector through a mirror mounted on the head coil.

Participants completed five functional runs of the set-shifting task. They either viewed trials or instruction cues (the word “STAY” or “CHANGE” in the center of the screen with a circle and a square on either the left or right of the word). Trials presented one of the target stimuli (circle or square), and children responded with a button press that mapped onto the spatial location of the target. Children were instructed to press the button as fast and as accurately as possible. See Figure 1.

Each of the five functional runs lasted three minutes 16 seconds (16 minutes 20 seconds total) and consisted of 6 epochs of Stay and Switch with an event-related trial structure. Each run included 6 Stay and 6 Switch instruction cues and 30 Switch and Stay trials with a

block lasting from 4 to 6 trials (150 Switch and 150 Stay trials total); block length was varied (12000ms to 21000ms) to reduce expectations of when a change would occur. Fixations (+) were interspersed to optimize the estimation of the hemodynamic response using OPTSEQ2 (Dale, 1999), and occurred in 500ms intervals ranging from 500 to 6000ms. Each trial began with the visual display of an instruction cue or trial for 1800ms, and then a fixation ('+') for 200ms. We analyzed the last two trials in a Stay epoch to capture the trials where children were most likely to be 'in set'; this was compared to the first two trials of a Switch epoch in an effort to capture the trials where switching is most difficult. Thus a total of 60 Stay and 60 Switch trials were compared across the five runs or 54 and 54 for children with four runs.

Behavioral Data Analysis

To compare the groups' switch costs, we calculated both accuracy and RT for the last two Stay and first two Switch trials in each block (60 per condition), using a repeated measures analysis of variance (ANOVA) with condition (Stay and Switch) as a within-participants repeated factor (Stay and Switch) and group (ASD and TDC) as the between-participants factor. Planned follow-up analyses included comparing groups on two 'switch cost' variables: one for accuracy (Stay accuracy – Switch accuracy) and one for RT (Switch mean RT – Stay mean RT). Larger switch cost scores correspond to greater difficulty switching between the two response sets.

Imaging procedure

All imaging data were collected on a Siemens Trio 3T MRI scanner (Erlangen, Germany) with a Total Imaging Matrix Upgrade and an 8-channel headcoil. A High resolution T1-weighted image was acquired using a 3D MPRAGE sequence (5 minute scan) with the following parameters: TR=2530, TE=3.5ms, 256×256mm FOV, 176mm slab with 1 mm thick slices, 256×256×176 matrix (effective resolution is 1.0 mm³), 1 excitation, and a 7° flip angle. Functional images were acquired using a T2*-sensitive gradient echo pulse sequence with the following parameters: time repetition=2000ms, time echo=30ms, 256×256 mm field of view, 64×64 acquisition matrix (for an in plane resolution of 3 mm), and a 90° flip angle. Forty-three 2.7-mm thick axial slices were acquired in descending interleaved axial slices (width=2.7mm, gap width=0.3mm, effective width=3mm) for 100 time points in each run (the first 2 volumes were included for signal stabilization and were discarded from analysis), and 60 acquisitions per task condition across the whole study.

fMRI preprocessing and first-level (time series) analysis

Functional image processing and statistical analyses were implemented primarily using FEAT (FMRIB's Expert Analysis Tool), part of FMRIB's Software Library (FSL) package (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). Each time series was despiked using AFNI's 3ddespike program (Cox, 1996), motion-corrected, temporally filtered (nonlinear high-pass filter with a 1/90 HZ cutoff calculated with FSL's cutoffcalc), and a 3D Gaussian filter (FWHM=6mm) was applied to account for individual differences in morphology and local variations in noise. Voxel-wise regression analyses were performed on each of the participant's five runs using FILM (FMRIB's Improved Linear Model). Each trial type (Stay trials and Switch trials) was coded as an explanatory

variable and convolved with a double gamma function to approximate the time course of the blood-oxygen dependent hemodynamic response. Each explanatory variable yielded a per-voxel parameter estimate (PE or beta map) that represented the activation magnitude associated with that variable. FMRIB's Linear Image Registration Tool (FLIRT) transformed each run's functional activation maps and their corresponding structural MRI maps into stereotactic space (MNI) with an affine transformation that used 12° of freedom.

Individual and group-level analyses

Using FEAT, all runs were entered into a second-level analysis using FSL's mixed effects models to generate a subject-level average map for Switch+Stay Trials>Fixation and Switch Trials>Stay Trials. Within and Between-group level analyses used FSL's Linear Analysis of Mixed Effects 1+2 model. The z (Gaussianized T) statistical maps were cluster corrected with a voxel z score >2.6 , and a cluster-corrected significance threshold of $p < 0.05$ (Worsley, 2001). Brain activation was extensive in the ASD and TDC groups, so a voxel z score >3.5 (cluster-corrected at $p < 0.05$) was used for localization purposes. We explored brain-behavior relationships by correlating functional clusters that differed between groups in the Switch vs. Stay contrast with switch costs derived from response times (RT) and ASD diagnostic symptom scores. We used Spearman's rho – a non-parametric rank-order correlation – to minimize the influence of outliers for RT data and to account for the non-continuous nature of ADOS scores.

Results

Behavioral Performance

For accuracy, there was a main effect of Condition $F(1,37)=4.62$, $p < 0.05$, $\eta^2_p=0.11$, and a main effect of Group, $F(1,37)=13.08$, $p < 0.01$, $d=1.19$, but no significant Group $\times$ Condition interaction, $F(1,37)=1.08$, $p=0.31$, $\eta^2_p=0.03$. Accuracy was lower on Switch trials ($M=91\%$, $SD=8.1$) than Stay trials ($M=93\%$, $SD=6.1$). The ASD group had a significantly lower overall accuracy than the TDC group (See Table 2). For RT, there was a main effect of Condition, with Switch trials ($M=686\text{ms}$, $SD=112\text{ms}$) being slower than Stay trials ($M=662\text{ms}$, $SD=103\text{ms}$), $F(1,37)=9.58$, $p < 0.01$, $\eta^2_p=0.21$, but no significant effect of Group, $F(1,37)=0.16$, $p=0.69$, $d=0.12$, and no significant Group $\times$ Condition interaction, $F(1,37)=0.95$, $p=0.34$, $\eta^2_p=0.03$. Our *a priori* hypothesis was to probe for group differences in switch cost, therefore we conducted follow-up analyses of the within-group differences in switch conditions, which revealed no significant group differences in accuracy switch cost, $t(37)=1.04$, $p=0.31$, $d=0.33$, or in RT switch cost, $t(37)=0.98$, $p=.034$, $d=0.32$ (See Table 2 for means). Thus, the behavioral data demonstrate that the task elicits a significant switch cost in accuracy and RT. The ASD group was less accurate overall than the TDC group, and the predicted Group $\times$ Switch Condition interactions were in the expected direction but were small, non-significant effects.

Brain Imaging: Analysis of Task-related Activation

We examined activation that was associated with general task engagement. We compared activation across both Switch and Stay trials relative to Fixation in each group and then differences across groups. The Switch+Stay trials>Fixation contrast in each group revealed

activation in expected salience, visual processing and motor regions. The TDC group showed significant activation in bilateral insula, mid-dorsal cingulate/supplementary motor area (mdACC/SMA), bilateral putamen, primary motor and areas, and bilateral cerebellum. The ASD group showed significant activation in a cluster spanning the right central operculum, inferior frontal gyrus, insula, and putamen, as well as a second cluster spanning the cingulate/SMA. See Supplementary Figure 1a and 1b and Table S1. No group differences emerged at our original threshold of $z > 2.6$, $p < 0.05$, so we used a more liberal threshold of $z > 3$ (uncorrected). Compared to the TDC group, the ASD group demonstrated decreased activation in a cluster covering the middle temporal gyrus. The ASD group did not demonstrate increased activation in any regions compared to controls.

Brain Imaging: Set-shifting Activation

The Switch vs. Stay contrast in each group revealed activation in predicted regions. Both groups activated bilateral middle frontal gyrus (MFG)/frontal pole, right lateral superior frontal gyrus (SFG)/precentral gyrus, bilateral putamen, mdACC/SMA, medial SFG, right insula, bilateral superior parietal lobule, precuneus, cuneus, and bilateral cerebellum. Only the TDC group activated left lateral SFG/precentral gyrus, left insula, left hippocampus, left fusiform/inferior temporal/parahippocampal area, and bilateral occipital regions. Only the ASD group activated right inferior frontal gyrus (IFG) and right thalamus. Direct comparison, however, revealed significantly greater activation in the ASD group for the Switch vs. Stay trial contrast in the following regions: mdCC/SFG, left MFG/frontal pole, and right IFG. The TDC group did not show any regions with increased activation compared to the ASD group. See Figure 2 and Table 3 for detailed listings of peak voxel coordinates, Brodmann Areas, and cluster sizes.

Brain-Behavior Correlations

Correlation analyses between mdCC/SMA, right IFG, and left MFG with the RT switch cost, and middle temporal gyrus with overall accuracy resulted in small, non-significant effects within and across groups, ($r_s \leq .30$, p 's > 0.21). Correlations with the ADOS diagnostic algorithm were also non-significant, ($r_s \leq .39$, p 's > 0.09).

Discussion

Children with ASD demonstrated similar set-shifting performance as TDCs on a tightly controlled, low-level set-shifting task, and this was accompanied by activation in executive circuitry thought to govern set-shifting. Specifically, both groups were slower and more error prone on the Switch trials compared to Stay trials, indicating that response reconfiguration is effortful. Compared to TDCs, the ASD group had significantly lower overall accuracy, but in contrast to our predictions, the ASD group did not demonstrate a significantly greater switch cost. This finding suggests that the switching component of the task was equally effortful for both groups. Both groups engaged the putative network of bilateral MFG, IFG, cingulate, bilateral striatum, bilateral parietal, and cerebellum regions for the Switch vs. Stay trial comparison. Direct group comparisons revealed that the ASD group had greater activation in the mdACC/SFG, left MFG, and right IFG than the TDC

group. Correlation analyses between brain activation and behavior revealed non-significant, small effects.

The present findings replicate and extend the existing fMRI literature of set-shifting in ASD. First, our finding of similar switch costs and increased brain activation in frontal regions for the ASD group replicates a prior adult study (Schmitz et al., 2006) and extends it to a younger age group. Second, this study provides an assessment of the first of four levels of set-shifting while minimizing non-shifting components. Third, our finding of decreased overall accuracy for the ASD group, and decreased activation in the middle temporal gyrus for the Switch+Stay trials>Fixation contrast may relate to a general task strategy. We discuss each of these points in turn.

Increased mdACC/SFG, left MFG and right IFG activation in children with ASD converges with a prior spatial set-shifting study of adults with ASD (Schmitz et al., 2006). Adults with ASD performed similarly to controls, and had greater activation in bilateral parietal regions. The mdACC/SFG regions have putative roles in selecting the correct action set (SFG) and in affiliating them with the appropriate consequences (mdACC) (Rushworth, Walton, Kennerley, & Bannerman, 2004). The MFG and IFG have been implicated in set-shifting for maintaining task relevant information (Buchsbaum et al., 2005; Crone, Donohue, et al., 2006; Garavan, 2002; MacDonald, Cohen, Stenger, & Carter, 2000; Monchi et al., 2001; Wager et al., 2004), as well as other executive processes, including working memory (Wager & Smith, 2003) and response inhibition (Aron et al., 2007). Both the present and prior adult study (Schmitz et al., 2006) minimized prepotent biases (by presenting the two response sets equally), and verbal working memory demands (by using visual cues that mapped the target to the same spatial location on the screen as the response button in the participant's hand), but did not eliminate these demands altogether. We speculate that the increased activity in the left MFG during switch trials may reflect maintenance of the current task rule (Buchsbaum et al., 2005; Garavan, 2002; MacDonald et al., 2000), while the greater right IFG activation may reflect inhibition of prior motor response sets affiliated with the old rule (Corbetta & Shulman, 2002; Durston et al., 2003). The present and prior two studies (Schmitz et al., 2006) suggest that when verbal working memory and prepotent biases are minimized, individuals with ASD demonstrate similar switch costs to controls; however, this intact switching performance requires greater activation of the executive function network in ASD to achieve the same performance as the control groups. This increased activation in ASD could be interpreted as a less efficient executive function network in children with ASD, because the increased activation was needed to perform as well as controls (Berl, Vaidya, & Gaillard, 2006).

Two other fMRI studies employed tasks which make broader executive function demands (Shafritz et al., 2008; Solomon et al., 2009). These studies demonstrated both reduced accuracy on switch trials and reduced activation in frontal, striatum, and parietal regions in ASD, one in adolescents and the other in adults. Both studies used tasks that established strong prepotent biases (75% and 94% of 'Stay'-type trials), and they required participants to either memorize abstract symbols for a rule set (Solomon et al., 2009) or remember a rule for an extended period of time (164 trials)(Shafritz et al., 2008). The oddball switching task completed by adults also required switching attention between targets across blocks as the

target shifted between a rarely presented circle or triangle (3% each) in comparison to the frequently presented square (94%) (Shafritz et al., 2008). These multiple shifting levels and non-shifting executive demands may have increased task difficulty.

Together, these four studies suggest that set-shifting impairments are highly task dependent in ASD. Intact behavioral performance accompanied by greater activation in frontal or parietal regions in ASD groups occurs when set-shift cues include a concrete spatial location-response button mapping (Schmitz et al., 2006 and present study). This increased activation may reflect greater engagement of spatial mapping/stimulus reappraisal (parietal) or stimulus-response maintenance (MFG and IFG). However, set-shifting performance is impaired when verbal working memory demands are increased by learning abstract symbols to reference rules and responses, and when a strong prepotent bias is established for one of the two task sets. Impaired performance is paired with reduced activation of the frontal, striatum, parietal, and temporal regions (Shafritz et al., 2008; Solomon et al., 2009). This decreased activation may reflect an overloading of executive circuitry that governs set-shifting. Prior behavioral studies suggest that abstract rules (Bíró & Russell, 2001) and task complexity (Minshew, Goldstein, & Siegel, 1997) are driving forces of impaired set-shifting performance in ASD, and the brain imaging data supports this interpretation. Thus, the complicated history of both intact and impaired behavioral performance across a number of card sorting, reversal, and open-ended set-shifting tasks in school-age children may be partially explained by differences in task characteristics (D'Cruz et al., 2013; de Vries & Geurts, 2012; Goldberg et al., 2005; Hughes et al., 1994; Landa & Goldberg, 2005; Poljac et al., 2010; Solomon et al., 2008; Van Eylen et al., 2011; Williams & Jarrold, 2013; Yerys, Wallace, et al., 2009; Yerys et al., 2012).

The present study suggests that the lowest shifting level - response reconfiguration – does not elicit flexibility performance deficits; however the increased frontal activation observed in the ASD group suggests that completing even the simplest form of set-shifting is more computationally intensive. Greater frontal activation at the response reconfiguration shifting level in ASD may start a ‘snowball’ effect. As individuals with ASD encounter more complex forms of shifting, like switching between competing labels for a single stimulus in a lab task (“red” vs. circle”) or changing their approach to solving a differential equation, their remaining neural resources may be overwhelmed, leading to impaired task performance. Thus, performance based deficits may only become apparent when set-shifting tasks are more demanding. Future studies can test whether any of the remaining shifting levels or specific combinations of levels (e.g., response reconfiguration and attention switching vs. response reconfiguration and stimulus reappraisal), as well as non-shifting demands (e.g., verbal working memory, prepotent bias strength) are necessary and sufficient to elicit poor set-shifting performance in ASD. Unmasking the critical elements that lead to successful or unsuccessful set-shifting will assist the field in refining flexibility interventions (Kenworthy et al., 2013).

The ASD group made more errors than the TDC group, which suggests that the task was harder for them. However, the ASD group's overall accuracy was high (89%). The variability in overall accuracy is likely driven by factors related to clinical status within the ASD group. This behavioral finding was accompanied by a marginal finding of reduced

activation in the right middle temporal gyrus. This area has a role in language processing due to its direct connection with Broca's Area in human and non-human primates (Margulies & Petrides, 2013), and corroborating evidence of activation during set-shifting studies with strong verbal demands (verbal fluency and trailmaking test; Jacobson, Blanchard, Connolly, Cannon, & Garavan, 2011; Pauli et al., 2013). One possible explanation for the group difference in activation is that the TDC group may have engaged the region as part of a language-based strategy to perform the task, while the ASD group did not. This would be consistent with data from set-shifting and other executive function tasks that used articulatory suppression manipulations that degraded performance in TDC groups but not ASD (Wallace, Silvers, Martin, & Kenworthy, 2009; Whitehouse, Maybery, & Durkin, 2006; Williams, Bowler, & Jarrold, 2012).

Future neuroimaging studies should recruit larger samples to provide a better sampling (and brain-behavior correlation) of the continuum of rigid behaviors in ASD. The present study was also constrained by an ASD cohort with above average cognitive functioning (i.e., Full-Scale IQ $M=116$). This subset of the ASD population likely has cognitive resources that place them in a unique position to perform well on tasks tapping low level shifting, despite struggling with more complex set-shifting impairments in everyday settings (Gioia et al., 2002; Kenworthy et al., 2005; Rosenthal et al., 2013).

In summary, frontal, striatum, parietal, and cerebellar regions were sensitive to response reconfiguration in children with ASD using a set-shifting task. Furthermore, engaging in an executive task was generally more difficult for children with ASD, and that was reflected in lower accuracy and decreased activation in the right middle temporal gyrus. Our findings suggest that this most basic level of set-shifting is intact in children with ASD relative to controls at the behavioral level when non-shifting demands are minimized; however the lateral prefrontal and superior medial prefrontal regions are activated to a greater degree in ASD reflecting inefficient functioning of executive circuitry. Thus, impaired performance on other set-shifting tasks may arise from the combination of multiple levels of set-shifting and non-shifting demands that incrementally (or exponentially) tax neural resources. These findings are important for our understanding, not only of the biological basis of set-shifting in the developing brain in ASD, but also of the nature of behavioral inflexibility in ASD. Inflexibility is an important target for treatment in ASD (Kenworthy et al., 2013). To the extent that we can parse intact from impaired aspects of flexibility, we can focus treatments more effectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. The set-shifting task

Instruction cues show the spatial mapping of stimuli to response buttons in the participant's left and right hands. For example, when the circle was on the right side of the instruction cue, then the child responded to circle trials with a right-handed button press. They are enlarged for readability but stimuli are the same size in the experiment. The word 'Stay' was presented in blue and 'Switch' was presented in red in order to increase the salience of the rule. For statistical analysis we analyzed the behavioral performance and neural correlates affiliated with the final two trials in the Stay blocks and the first two trials in Switch blocks.

Figure 2.

Brain activation for the Switch>Stay contrast in the TDC (a), ASD (b), and ASD>TDC (c) analyses. Both groups show activation in multiple frontal, striatum, parietal, temporal, and cerebellar regions. The ASD group has significantly greater activation in a cluster crossing the mid-dorsal anterior cingulate cortex and superior frontal gyrus, a cluster in left middle frontal gyrus, and a cluster in right inferior frontal gyrus. All Images are thresholded at a voxel z score >2.6 , and cluster-corrected at $p < 0.05$.

Table 1

Participant characteristics by diagnostic group.

	TDC (n=19)	ASD (n=20)	p-value
Age (years) <i>M</i> (<i>SD</i>)	11.36 (1.54)	11.32 (1.84)	0.94
Age Range	7.17 - 13.33	7.28 - 14.00	
FSIQ (SS) <i>M</i> (<i>SD</i>)	119.58 (13.25)	114.70 (14.50)	0.28
FSIQ Range	104 - 144	83 - 138	
Sex-Ratio (M:F)	13:6	16:4	0.41
ADOS Social+Communication	--	11.15 (2.92)	
ADI-R Social Interaction *	--	19.33 (3.82)	
ADI-R Communication *	--	14.06 (4.41)	
ADI-R Repetitive Behaviors *	--	4.39 (1.72)	

FSIQ=Full-Scale IQ

SS=Standard Score (*M*=100; *SD*=15)

SRS= Social Responsiveness Scale

ADOS=Autism Diagnostic Observation Scale Module 3

ADI-R=Autism Diagnostic Interview - Revised

*
N=18

Table 2

Set-Shifting performance separated by diagnostic group and condition

	TDC (n=19) <i>M(SD)</i>	ASD (n=20) <i>M(SD)</i>	<i>p</i>-value
Overall Accuracy (%)	95.9 (3.0)	89.3 (7.3)	<0.01
Overall RT (ms)	667 (91)	680 (119)	0.84
Stay Accuracy	96.4 (3.7)	90.9 (6.9)	<0.01
Switch Accuracy	95.3 (4.6)	87.8 (9.0)	<0.01
Stay RT (ms)	659 (85)	665 (121)	0.85
Switch RT (ms)	675 (99)	696 (125)	0.56
Switch Cost Accuracy	1.1 (5.6)	3.1 (6.5)	0.31
Switch Cost RT (ms)	16 (33)	31 (58)	0.34

Table 3

Brain activation for the Switch vs. Stay Contrast by diagnostic group and group differences

	Activated Region	BA	Peak MNI Coordinate			Voxels	Peak z-score
			X	Y	Z		
TDC							
	Precuneus/SPL/SG/AG/Cuneus	7/40/39	4	−66	54	9410	10.9
	Occipital Pole/OFG	18/37	40	−67	−15	2617	7.23
	SMA/mdCC	6/32/24	−2	−2	52	1730	6.74
	Occipital Pole/LOC/ OFG	18	−24	−100	−2	1669	7.35
	Putamen	-	−26	2	4	562	5.85
	Frontal Pole/MFG	10/9	−32	42	18	495	5.04
	Putamen/Insula	13	26	8	0	400	5.80
	MFG/SFG/PcG	6	30	2	60	391	6.81
	Frontal Pole	10	38	56	12	325	4.90
	Posterior Cingulate	23	10	−32	26	107	5.10
	Hippocampus	-	−20	−38	6	106	5.61
	MFG	9	50	30	30	81	4.94
	Fusiform/ITG/parahippocampus	37/36	−38	−40	−10	78	4.95
	MFG/Frontal Pole	9	32	34	24	73	4.75
ASD							
	LOC/Precuneus/SG/AG/SPL	7/39/18/40	−14	−72	56	15156	8.60
	SMA/MFG/SFG/mdACC	6/9/8/24/32	0	8	50	7612	7.36
	Frontal Pole/MFG	10/9	38	56	14	1236	6.39
	Insula/Putamen/Thalamus	13	−32	18	4	1168	6.30
	Posterior Cingulate	23	2	−36	20	617	5.61
	Thalamus/Putamen	-	18	−26	12	587	5.93
	MFG/PcG	6/8	−46	8	50	378	3.98
ASD>TDC	SFG/mdACC	8/32	−10	18	46	364	4.34
	IFG/PG	44/45	50	20	14	324	4.1

AG=Angular Gyrus, BA= Brodmann's Area, IFG=Inferior Frontal Gyrus, IPL=Inferior Parietal Lobule, ITG=Inferior Temporal Gyrus, LOC=Lateral Occipital Cortex, mdACC=mid-dorsal Anterior Cingulate Cortex, MFG=Middle Frontal Gyrus, OFG=Occipital Fusiform Gyrus, SFG=Superior Frontal Gyrus, PcG=Precentral Gyrus, SMA=Supplementary Motor Area, SG=Supramarginal Gyrus, SPL=Superior Parietal Lobule