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Aberrant neural mediation of verbal fluency in Autism Spectrum Disorders

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Abstract

Objective: Contrasts of verbal fluency and automatic speech provide an opportunity to evaluate the neural underpinnings of generativity and flexibility in autism spectrum disorders (ASD).

Method: We used functional magnetic resonance imaging (fMRI) to contrast brain activity in high functioning ASD (n=17, mean verbal IQ=117) and neurotypical (NT; n=20, mean verbal IQ=112) adolescent and young adult males (12-23 years). Participants responded to three word generation conditions: automatic speech (reciting months), category fluency, and letter fluency.

Results: Our paradigm closely mirrored behavioral fluency tasks by requiring overt, free recall word generation while controlling for differences in verbal output between the groups and systematically increasing the task demand. The ASD group showed reduced neural response compared to the NT participants during fluency tasks in multiple regions of left anterior and posterior cortices, and sub-cortical structures. Six of these regions fell in corticostriatal circuits previously linked to repetitive behaviors (Langen, et al, 2011), and activity in two of them (putamen and thalamus) was negatively correlated with autism repetitive behavior symptoms in the ASD group. In addition, response in left inferior frontal gyrus was differentially modulated in the ASD, relative to the NT, group as a function of task demand.

Conclusions: These data indicate a specific, atypical brain response in ASD to demanding generativity tasks that may have relevance to repetitive behavior symptoms in ASD as well as to difficulties generating original verbal responses.

Keywords

autism; verbal fluency; fMRI; executive function; left inferior frontal gyrus

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1.1 Introduction

Verbal fluency tasks measure the ability to generate lists of words aloud under time constraint to letter cues (phonemic, or letter, fluency, e.g., “tell me all the words you can think of that begin with the letter A”) or conceptual category cues (semantic, or category, fluency, e.g., “tell me all the animals you can think of”). People with ASD typically struggle with verbal fluency (Geurts et al., 2004; Spek et al., 2009; Turner, 1999; Verté et al., 2005), particularly letter fluency, when compared to individuals of the same verbal ability (Boucher, 1988; Geurts and Vissers, 2012; Kiliñcaslan et al., 2010; Kleinhans et al., 2005; Robinson et al., 2009; Rumsey and Hamburger, 1988), or to their own word knowledge (Kenworthy et al., 2005).

Verbal fluency deficits are related to impaired executive function (EF), and hypothesized to specifically represent deficits in generativity, flexibility/inhibition, organization, strategic lexical search, and monitoring (Turner, 1999). Other EF abilities, such as working memory, are also required for successful verbal fluency performance as the words already spoken must be held in mind during word generation. Generativity, flexibility and organization have been consistently identified as impaired in ASD (Turner, 1995; Kenworthy et al., 2005; for review see Hill, 2004 and Kenworthy et al., 2008). Pennington and Ozonoff (1996) report larger effect sizes for flexibility deficits in ASD than for other domains of EF in a range of developmental disorders. Accordingly, verbal fluency tasks may be useful for investigating the neural substrate of EF in ASD.

There are a handful of fMRI investigations in ASD of EF domains that may relate to verbal fluency performance, such as flexibility, inhibition, and working memory. The task demands of flexibility, inhibition and working memory measures are specific and rely on distinct neural networks (Gilbert et al., 2008). However, the evidence also supports a general pattern of under-activation in ASD, compared to control, participants in fronto-striatal-parietal networks related to EF (Robbins, 2007; Rubia et al., 2007; Wager et al., 2004; Wager and Smith, 2003). Shafritz et al. (2008) report reduced activation in frontal, striatal, and parietal regions in response to a visual flexibility task in adolescents/young adults with autism compared to neurotypical (NT) controls. Although presented as a cognitive flexibility task, the measure was multiply determined, like many EF tasks. It required maintenance of a stimulus-response rule in working memory, and inhibition of pre-potent responses, as well as the periodic shifting of stimulus-response rules. Kana et al. (2007) document reduced neural activity in the anterior cingulate in adults with ASD compared to NT controls on an inhibition task. In adolescents with ASD, Solomon et al. (2009) found reduced neural activity in frontal and parietal areas during a task requiring inhibition of pre-potent responses and working memory. Koshino et al. (2008) report reduced activation in ASD compared to controls in the left inferior frontal gyrus (LIFG) and dorsolateral prefrontal cortex (DLPFC) during an n-back working memory task with letter stimuli. The authors hypothesize that in contrast to NT participants, the ASD participants processed the letters as visual, not verbal stimuli.

The exception to this pattern of reduced activity during EF tasks in ASD is reported by Schmitz and colleagues (2006). They found *increased* activity in adults with ASD compared to controls during inhibition Go/No-go and interference tasks (left inferior and orbital frontal gyrus, and left insula); and a flexibility task (right inferior and left mesial parietal lobes). It is notable that all of the tasks described above present visual stimuli and require a motor response, thus EF has been explored in ASD in the context of tasks that encourage nonverbal problem solving.

Atypical neural activity in the LIFG has been described in ASD during a variety of language-related tasks, such as sentence comprehension (Just et al., 2004; Kana et al., 2006; Tesink et al., 2011) and single word semantic decisions (Gaffrey et al., 2007; Harris et al., 2006). However, we are aware of only two fMRI investigations of language-based measures of EF in ASD, both of which use a verbal fluency task. Kleinhans and colleagues (2008) found equivalent activation of the left prefrontal cortex during both category and letter fluency in ASD and NT control groups, but greater leftward asymmetry in controls than in ASD. Interpretations of these findings are complicated by the fact that the ASD and control groups spanned wide age ranges (14-44 years) and were not matched for verbal intelligence or fluency performance. In a study of sex differences, a group of ASD adults with equal representation of males and females showed increased activation in the LIFG (BA 47), left inferior parietal lobe and left middle occipital gyrus compared to control participants (Beacher et al., 2012). The groups were matched for sex ratio, but not intelligence. The ASD group had significantly lower reading scores than the control group. The use of a covert fluency paradigm, in which the participants were instructed to think of words to letter cues, also complicates interpretation of results as there is no direct measure of performance.

A tightly controlled comparison of well matched adolescents/young adults with ASD and NT controls on measures of verbal fluency would allow investigation of EF in the language modality. A contrast of automatic speech to fluency, and category fluency to letter fluency, should reveal coordinated activity of a number of brain areas, particularly in the frontal and temporal lobes of the left hemisphere. Damage to the left frontal lobe, especially to LIFG, has consistently been shown to impair verbal fluency, even in patients who are not overtly aphasic (e.g., Baldo and Shimamura, 1998; Milner, 1964; Thompson-Schill et al., 1998). In addition, there is evidence that the generation of word lists to letter cues relies on a partially different network of brain regions than the generation of word lists to category cues. Studies have shown, for example, that frontal lobe damage results in disproportionate impairment to letter fluency (e.g., Baldo et al., 2001; Hodges et al., 1999; Miller, 1984), while temporal lobe damage impairs category fluency more than letter fluency (e.g., Baldo et al., 2006; Butters et al., 1987; Hodges et al., 1999; Monsch et al., 1994). Functional neuroimaging studies, using positron emission tomography (Gourovitch et al., 2000; Mummery et al., 1996) and fMRI (e.g., Costafreda et al., 2006; Perani et al., 2003) have generally supported these findings. In addition, requiring individuals to switch between two word retrieval cues during fluency adds an explicit flexibility demand that increased difficulty for individuals with ASD in a behavioral study (Kleinhans et al., 2005). This switching condition should put increased demands on parietal neural circuitry previously associated with flexibility tasks (Shafritz et al., 2008; Schmitz et al., 2006).

In the present study, we investigated the neural correlates of verbal fluency performance in adolescent and young adult males with ASD compared to a group of NT males matched for age and verbal intelligence. There were five task conditions: four fluency conditions and an automatic speech condition. In the latter, participants continuously produced an over-learned sequence of words (recited the months of the year) to provide a word generation baseline and control for language output effects. The four fluency conditions required free recall word generation to letter and category cues with and without an exogenous switching manipulation. In the switching condition participants were required to alternate retrieval according to two cues (two letters or two categories). We attempted to control for performance differences between the groups by requiring overt word generation over short, 10 second blocks of time. We have previously shown that this design allows for the minimization of speech-related motion artifacts using a standard regression analysis that exploits the delay in task induced changes in BOLD as compared to motion induced signal changes (Birn et al., 2004). By requiring participants to speak aloud during the task we were

able to measure task performance, as well as more accurately represent the task parameters of standard fluency paradigms.

We previously used this paradigm in NT adults (Birn et al., 2010) and found expected activations in the left hemisphere during the fluency tasks, and greater right hemisphere activation during the automatic speech condition. We also found expected differences between the fluency types with differential involvement of frontal and temporal lobe regions for letter fluency and category fluency, respectively. The additional task demand of alternating between two categories or two letters resulted in greater neural activity in bilateral regions of dorsal (precentral and superior parietal cortex) and ventral (fusiform gyrus) cortices. Based on previous work we expected that when compared to NT controls, ASD participants would reveal weaker recruitment of frontal (LIFG)-striatal-parietal neural networks during contrasts of automatic speech versus fluency and category fluency versus letter fluency. We expected that the switching condition would accentuate the activation differences between ASD and NT participants, particularly in parietal cortices.

There is some evidence linking repetitive, restricted behaviors and interests autism symptoms (RRBI) and EF deficits on fluency and flexibility tasks. Turner (1999) argues that generativity deficits limit spontaneous behavior and increase RRBI, and points to evidence of a negative correlation between ideational and design fluency performance and rates of repetitive behavior in people with ASD (Turner, 1997). We were unable to replicate that finding using the category fluency task (Kenworthy et al., 2009), but we and others have documented a positive relationship between cognitive inflexibility and RRBI using nonverbal measures of flexibility (Lopez et al., 2005; South et al., 2007; Yerys et al., 2009). Exploration of the linkage between functional brain activation during EF related tasks and autism symptoms is an important (Schmitz et al., 2006), if understudied question. Schafritz et al. (2008) report that activation during a flexibility task in ASD participants within anterior cingulate cortex (ACC) and posterior parietal regions declined significantly as the severity of RRBI increased. In order to approach the question of whether brain activity during fluency is related to RRBI, we applied a theory driven method building on Langen and colleagues' (2011) work linking three parallel corticostriatal macro-circuits, sensorimotor, associate and limbic (Alexander et al., 1986), to repetitive behavior symptoms. Each of these circuits contains specific nodes within the frontal cortex, striatum, pallidum and thalamus. Because all of the networks proposed by Langen et al. are linked to aspects of RRBI, we did not restrict our inquiry to any one of them *a priori*, but instead chose to investigate correlations between RRBI symptoms and the broader brain regions that contain all three loops. We constrained analyses of the relationship of RRBI and brain activity during fluency tasks in ASD to areas that: show different neural response to fluency demands in ASD than NT participants, and are in the frontal cortex, striatum, pallidum or thalamus.

This study does not directly investigate patterns of correlation in brain activity between regions because the data for the current study were used in a previous methodological investigation that evaluated multiple approaches for determining group differences in "functional connectivity" in ASD (Jones et al., 2010). That report focused on issues concerning measuring co-variation in neural signals between brain sites after regressing out task-related fluctuations in activity. It also reported decreased correlation in ASD compared to NT individuals between brain regions involved in performing the fluency tasks. Specifically, correlations were lower in the ASD group between LIFG and left fusiform gyrus, and between LIFG and left inferior parietal lobule. This pattern of results was observed after removal of all task-related effects, indicating that the differences in correlations between the groups were not driven by task specific responses. These findings are integrated with those of the present study in the Discussion.

1.2 Material and Methods

1.2.1 Participants

Twenty neurotypical (NT) males (12-21 years old) and 24 high-functioning males with ASD (12-23 years old) participated in the experiment, though seven ASD participants were subsequently excluded from analyses as explained below. NT participants were not entered in the study if they had: been given a psychiatric diagnosis; ever received mental health treatment for anxiety, depression, or any other psychiatric condition; taken psychotropic medications; required special services in school; or had trauma/injury that could potentially affect cognitive functioning and/or brain development. Diagnoses of ASD were confirmed by expert clinical impression using the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (*DSMIV-TR*; American Psychiatric Association, 2000), and results from research valid administrations of the Autism Diagnostic Interview (ADI-R; Lord et al., 1994), and Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). The ADI-R is a parent interview measure that queries presence or absence of autism symptoms in childhood. The ADOS is a semi-structured, standardized assessment of communication, social interaction and repetitive behaviors and interests. Eleven participants in the ASD group were taking one or more psychotropic medications, as detailed in Jones et al. (2010). With the exception of one excluded ASD participant, all full-scale IQ scores were 85 as measured by a Wechsler Intelligence Scale. The groups did not differ on full-scale, verbal or performance IQ, age or handedness (Table 1). Six additional ASD participants were excluded due to: scanner malfunction ($n=1$), uncorrectable susceptibility artifact (braces; $n=1$), lack of behavioral responses during the majority of the runs ($n=1$), and excessive head motion ($n=3$) resulting in a final sample of 17 ASD participants. No NT participants were excluded. Informed written assent and consent were obtained from all participants and/or their parent/guardian when appropriate in accordance with a National Institutes of Health Institutional Review Board-approved protocol.

1.2.2 Imaging and Task Parameters

Participants were scanned on a 3 Tesla general Electric MRI scanner using a quadrature birdcage RF head coil (GE Medical, Waukesha, WI), with TR/TE=2000 ms/30 ms, resolution: $3.8 \times 3.8 \times 5 \text{ mm}^3$, 115 time points per run, and eight runs per imaging session. Each subject's head was immobilized using a vacuum pillow (S&S Par Scientific, Houston, TX, USA). During the imaging runs, participants performed a self-paced overt verbal fluency task. The task was performed in a blocked design, with 10 second periods of task performance alternated with 10 second periods of rest (participants were instructed to stare at a central fixation cross). Using this design, blood oxygenation level dependent (BOLD) signal changes are delayed by a quarter cycle relative to the motion-induced signal changes, which occur in synchrony with the task. As a result, the correlation between BOLD and motion-induced signal changes is small, and the number of false positives resulting from speech-related motion artifacts (when performing a standard regression analysis) is minimized (for details see Birn et al., 2004).

In each 10 second block, participants were presented with one of five possible written task cues: a single letter, a single category, two letters, two categories, or the word “months”. For each of these cues, they were asked to generate as many words as possible until the fixation cross appeared. Written cue letters or words were presented in the center of the screen and remained visible for the duration of the 10 second block. In the months condition participants named the months of the year in chronological order starting from “January.” When presented with a single letter or category, participants were asked to generate as many words as they could think of starting with that letter, or that were members of the category, until the fixation cross appeared (and the letter or word disappeared). When presented with

two letters or two categories, participants were required to generate one word corresponding to one of the letters or categories, then switch to the other letter or category, and continue to alternate between the two cues (e.g., when presented with the cue “color/fruit” participants would generate words such as “blue, apple, red, banana...”). Before entering the scanner, participants were shown sample task stimuli on a laptop, and given specific instructions for each task. They then practiced each task to demonstrate their understanding of it before entering the scanner.

During imaging, each fluency condition was presented twice, in random order, in each of 8 runs for a total of 16 unique blocks for each of the letter and category conditions. The participants’ spoken responses were recorded using an optical microphone with active noise cancellation (Optoacoustics, Ltd., Israel). This microphone and the associated processing software allowed the participants’ responses to be separated from the scanner sounds.

1.2.3 Data Analysis

Behavioral Data—The numbers of words produced in each condition were submitted to a Group (ASD, NT) $\times$ Task (months, one category, two categories, one letter, two letters) repeated measures analysis of variance (ANOVA).

Imaging Data—All image analyses were performed using AFNI (Cox, 1996). Reconstructed images were first corrected for bulk head motion using a rigidbody volume registration routine. Time series were then corrected for slicetiming differences, spatially smoothed using a Gaussian blur with a root-meansquare (RMS) width of 4mm, and converted to percent signal changes. Activation amplitudes for each condition were determined in each participant using a multiple regression analysis. Neural signal changes were modeled using the stimulus timing convolved with a gamma-variate (Cohen et al., 1997). Task-related motion artifacts were modeled using a boxcar waveform representing the task timing.

Data was analyzed with a mixed-effects repeated measures ANOVA with Group (ASD, NT) and Task (months, one category, two categories, one letter, two letters) as fixed factors, and participants as a random factor to evaluate the effects of the fluency conditions relative to automatic speech. A mixed-effects repeated measures ANOVA without the automatic speech condition was used to directly evaluate the main effects of Group (ASD, NT), Fluency Conditions (category, letter) and Switch demand (one cue, two cues). We constrained this analysis by creating a mask averaging all beta weights for each subject during fluency tasks with any activity above a baseline of 0 (threshold of $p < 10^{-6}$). Unless otherwise stated, all regions in this report were significant at a false discovery rate (FDR) corrected threshold ($q < .05$).

For regions that were underactive in the ASD group compared to the NT sample during fluency tasks and that fell within the cortical striatal networks proposed by Langen et al. (2011) to drive repetitive behavior, correlations were run between neural activation during fluency and total raw score on the ADOS Stereotyped Behaviors and Restricted Interests domain. The cortical striatal networks are comprised of the frontal cortex, striatum, pallidum and thalamus. Any region in which there was a main effect of group for level of brain activity during fluency (see Table 2) that fell within the areas defined by Langen et al. was included in the analysis. The ADOS raw score reflects examiner ratings of four behaviors: Unusual Sensory interests, Mannerisms, Excessive Interest in Specific Topics/Objects and Compulsions/Rituals.

1.3 Results

1.3.1 Behavior

As expected, the ANOVA revealed a main effect of Task ($p < .001$), largely due to participants producing more words when repeatedly reciting the months of the year than when producing words to letter or category cues (p 's $< .001$). Participants also tended to produce more words in response to one category cue than when switching between two category cues ($p < .001$), but more words in response to two letter cues than one letter cue ($p < .001$). In fact, fewer words were generated to the single letter cues than to all the other fluency conditions (p 's $< .005$), suggesting that this condition may have been most taxing on search and retrieval mechanisms. Importantly, neither the main effect of Group, nor the Group X Task interaction was significant ($p = 0.72$, and $p = 0.41$, respectively) (Figure 1). Although verbal fluency is a well established weakness in people with ASD, a difference in performance between the groups was not expected, because the groups were well matched for verbal intelligence and the response time was limited to 10 seconds. Behavioral studies reporting deficits on fluency tasks in ASD groups use the standard 60 second response time format, which requires the generation of many more words.

1.3.2 Imaging

Main Effects of Task—Neural activity in response to the different fluency conditions was highly consistent with our previous findings in an older group of NT individuals (Birn et al., 2010). Accordingly, we will describe these findings briefly and then turn to the critical comparisons of the ASD and NT groups. Relative to the automatic speech task (months), the fluency tasks yielded strongly left lateralized activity across wide expanses of posterior (left ventral occipitotemporal cortex, including the fusiform gyrus), and anterior cortices (Figure 2A). In these regions, the fluency tasks elicited more activity than automatic speech even though, on average, participants generated approximately three times as many words during the automatic than fluency task conditions. Activity in the majority of these regions was enhanced during letter, relative to category fluency (Figure 2B.) There were two main exceptions. First, there was greater activity for category than letter fluency in early visual areas (medial occipital cortices), likely due to the fact that whole words, rather than single letters, were presented on the screen during these conditions. Second, there was greater category-than letter-related activity in the left fusiform gyrus consistent with the need to retrieve words organized by object category (Martin, 2007). Finally, switching between two cues yielded enhanced activity in posterior parietal and ventral occipitotemporal cortices, relative to single cues (Figure 2C; see Birn et al., 2010 for a discussion of these findings).

Main Effects of Group—Against this background, group differences were found in multiple brain regions in which the ASD group showing reduced activation compared to the NT group (see Table 2 and Figure 3). No regions showed greater activity in the ASD than NT group. Six of the regions showing reduced activation in ASD compared to NT groups fell within the cortico-striatal networks linked to repetitive behavior by Langen et al. (2011). Three pre-motor regions were in frontal cortex locations described by Langen and colleagues (2011) (two in the LIFG, one in the left middle frontal gyrus) and three were subcortical (bilateral thalamus and putamen). Activity in two of the subcortical regions was significantly related to RRBI as measured by the ADOS. Specifically, increased RRBI were associated with reduced activity during fluency in the left thalamus ($Rho = -0.54$; $p = 0.013$) and the left putamen ($Rho = -0.41$; $p = 0.05$). Correlations between RRBI and activity in the right thalamus and one of the pre-motor LIFG regions ($-53\ 3\ 15$) trended toward, but did not reach, significance (Rho 's $= -0.33$, p 's $= .10$).

Group X Task Interactions—None of the interactions between group and condition was significant using FDR correction. At an uncorrected threshold of $p < .05$, however, both Group X Fluency Task, and Group X Fluency Task X Switch interactions were observed in the left inferior frontal gyrus. These interaction effects were particularly noteworthy because they occurred in the same LIFG region where we previously found activity to be significantly less correlated with left posterior cortical activity in this group of ASD participants (Jones et al., 2010). In fact, constraining the analysis to activation clusters that exceeded a threshold of 10 contiguous voxels in original imaging space ($\sim 703 \text{ mm}^3$) showed that these interactions were confined exclusively to the LIFG (cluster size 1503 mm^3 ; maximum voxel = $-51 +15 +10$; $t = 6.78$) (Figure 4). In this region, the ASD participants produced a more enhanced response during letter, relative to category fluency, than did the NT participants. An ANOVA of the responses averaged across all of the voxels in this LIFG region revealed a significant Group X Fluency Task interaction ($F=8.246$; $p < 0.01$) such that ASD participants showed a greater increase in activation from category to letter cues than NT participants (See Figure 4). Furthermore, this effect was particularly pronounced for the single letter cue condition. Specifically, there was a Group X Fluency Task X Switch interaction ($F= 6.043$; $p < 0.05$) characterized by significantly greater neural activity during the single, as compared to the two letter, cue condition for the ASD participants ($t = 3.313$, $p = 0.004$), but not for the NT individuals ($t = 0.77$; $p > 0.40$) (Figure 4).

1.4 Discussion

This is the first examination of which we are aware of the neural substrate of executive functions (EF) in the language modality in well matched high functioning adolescents and young adults with and without ASD. We compared the hemodynamic response during automatic speech (recitation of months), category and letter fluency tasks with and without a switch demand. Consistent with our study of NT adults, we found strong left-sided frontal and temporal cortical activations during fluency in contrast to the automatic speech condition, differential frontal and temporal lobe involvement in letter and category fluency, and increased parietal and ventral occipitotemporal activity when participants were required to shift between two different retrieval cues. Most important for our present considerations, there was reduced activity in multiple brain regions in the ASD compared to the NT group during fluency tasks even though the groups were equated on the number of words produced. Greater activity for the ASD than the NT group was not observed in any brain region.

Consistent with our hypotheses, the ASD group demonstrated reduced activity during fluency in frontal, striatal and thalamic, as well as cerebellar, regions associated with executive control networks in NT individuals (Robbins, 2007; Rubia et al., 2007; Wager et al., 2004; Wager and Smith, 2003). Furthermore, frontal and subcortical areas of reduced neural activity during fluency overlapped with several previous investigations of visual EF tasks in ASD which report reduced activity in the LIFG (Koshino et al., 2005; Koshino et al., 2008) the anterior cingulate cortex (Kana et al., 2007; Koshino et al., 2008; Shafritz et al., 2008), the striatum (Koshino et al., 2008; Shafritz et al., 2008) and thalamus (Koshino et al., 2008). Contrary to our predictions, and in contrast with findings in several other investigations of EF in ASD (Koshino et al., 2005, Shafritz et al., 2008; Solomon et al., 2009), we did not find differences between ASD and NT neural activations in the parietal lobe. We did elicit posterior parietal activity during the shift conditions of the fluency task as we expected based on previous studies of shifting during fluency tasks with NT participants (Birn et al., 2010; Gurd et al., 2002; Gurd et al., 2003), but we did not elicit group differences.

This discrepancy with other investigations of EF in ASD may reflect differences in task demand. In the present study, either one word or letter or two words or letters are presented throughout the task, giving participants a constant visual cue that indicates whether or not to shift. In contrast, Koshino et al. (2005), Shafritz et al. (2008), and Solomon et al. (2009) all introduce a rule or an instruction to shift that the participant must hold in mind and apply at the appropriate time. Although two of these tasks were not explicitly identified as measuring shifting, all of them place greater burden on the participant to initiate and maintain a shift without external supports than did our fluency switch condition.

Neural activity during letter fluency in two brain regions was related to RRBI in the ASD participants. Negative correlations were noted between fluency-related activity and RRBI in the putamen and ventral lateral nucleus of the thalamus, two nodes in the sensorimotor loop described by Langen et al. (2011) as linked to repetitive behaviors. The association of reduced putamen activity and increased severity of RRBI comes in the context of extensive evidence linking cortical-striatal circuitry and repetitive behavior symptoms in humans (see Langen et al. 2011 for review) and animals (Lewis et al., 2007). Enlarged basal ganglia have been described in multiple samples of individuals with ASD (e.g., Langen et al., 2007). Estes et al. (2011) report a negative correlation between RRBI and putamen and thalamic volumes in ASD. In a positron emission tomography study, Nakamura et al. (2010) linked reduction of serotonin transporter binding in the thalamus to RRBI in ASD. Thus, our findings provide further support for linking basal ganglia and thalamic abnormalities to generativity difficulties and repetitive behaviors in ASD (Turner, 1999).

We only partially confirm our hypothesis that RRBI in ASD is correlated with activity in brain regions that show abnormal neural response during fluency and are also contained within the corticostriatal macro-circuits proposed to drive repetitive behavior. Our failure to find such a relationship in frontal areas may reflect inadequacies in our measure of RRBI. The ADOS provides an approximately 45 minute observational window in which to observe RRBI, some of which might not be evident during that time period (Lord et al., 2000). Furthermore, it provides a non-continuous measure of behavior and requires non-parametric statistical analysis, potentially reducing power to detect a relationship. Concern about inadequate power to detect a relationship is heightened by the fact that there was a trend toward a significant correlation ($p=0.10$) between activity in pre-motor LIFG and RRBI. Future investigations should use a more rigorous measure of current repetitive behaviors that could parse motor stereotypies, rigidity and obsessions and compulsions, which are all associated with somewhat different networks in Langen and colleagues' theory (2011).

Other limitations of the current study include the wide age range of participants (12-23 years), and the fact that over half of the ASD participants were taking psychotropic medication. Age-related differences in brain structure in temporal cortex have been described in an overlapping group of adolescent and young adult participants with ASD (Wallace et al., 2012), but our relatively small sample size prevents us from investigating age-related differences in this study. We are likewise unable to address the role that medications may have played in brain activations observed in the ASD group.

Because the present study required overt verbal response from ASD and NT individuals who were well matched for verbal ability and verbal production during task performance, it provides novel data regarding the executive control of verbal output. It contrasts with previous executive control studies that have emphasized nonverbal problem solving or have not compared groups that were matched for verbal ability or output. As such, this study is particularly informative regarding the role of the LIFG in the executive control of language. In the LIFG, generally reduced activity during both the category and letter fluency tasks in ASD was limited to the *posterior*, premotor regions. Depressed LIFG activity in ASD has

previously been demonstrated during a variety of language as well as executive function tasks (e.g., Tesink et al., 2011). The locations of the LIFG regions in our study showing reduced activity in ASD ($-53 +3 +15$; $-42 0 +26$) are consistent with previous literature on language working memory functions (see Vigneau et al., 2006 for meta-analysis). The working memory demands of both category and letter fluency tasks are high, given the need to keep in mind the task rules and the words already produced. Our data are also consistent with findings associating ASD performance on working memory tasks with reduced neural activity in posterior LIFG compared to NT controls (Koshino et al., 2005).

In contrast, a complex pattern of results was noted in a more anterior region of the LIFG (pars triangularis, $-38, +20, +12$) which has been associated with domain general selection functions in NT individuals (Badre et al., 2005; Thompson-Schill et al., 1997; Thompson-Schill et al., 1998). In this region, the ASD participants demonstrated a disproportionate increase in neural activity for letter, relative to category fluency, compared to the NT individuals. Badre and Wagner's (2007) account of this area as serving a selection function that allows for the resolution of proactive interference, is consistent with the increased demands imposed by letter (vs. category) fluency. Our finding that this effect of increased LIFG activity in ASD was particularly pronounced for the single cue letter fluency condition is also consistent with this view. In this context, the presence of two letter cues from which to generate words may have made the task easier for the ASD participants by reducing the lexical search demand imposed by having to generate words to only one letter cue. Interestingly, Knaus and colleagues (2008) reported increased neural activity in ASD compared to typically developing adolescents in a similar region of the LIFG during a taxing word generation task. As in our study, the groups were matched for overall level of behavioral performance (Knaus et al., 2008).

Although subtle, this aberrant activity in the LIFG in ASD occurred in the context of decreased neural activity in the temporal lobes. One possible framework for understanding this discrepancy is connectivity. Findings of reduced connectivity in ASD are common (e.g., Gotts et al., 2012; Kana et al., 2006; Knaus et al., 2008; Sahyoun et al., 2010; Stigler et al., 2011; see Booth et al., 2011 and Müller et al., 2011 for reviews). We (Jones et al., 2010) found that the LIFG and the fusiform gyrus emerged as "under-connected" in ASD in the same dataset that we investigated here. Specifically, the LIFG site we now find associated with a disproportionately increased activity to letter (vs. category) fluency in the ASD (vs. NT group) was significantly less correlated with left fusiform activity in the ASD compared to the NT group. The fusiform site showing reduced correlation of activity with LIFG in ASD in our previous report overlaps with an area we now find to be underactive in ASD during fluency tasks. Taken as a whole, these data suggest a decreased coordination of activity in frontal control centers with key posterior cortical regions during verbal fluency in ASD.

These findings have implications for understanding the executive control of language production in ASD. They indicate a specific, atypical brain response in ASD to a demanding executive task that requires verbal output, which may have relevance to the functional deficits in generative language abilities observed in individuals with ASD. Formal language abilities are variable in children with ASD, who range from being nonverbal to having superior linguistic skills in many areas, but communication impairments are universal (Tager-Flusberg, 2006). Pragmatic language as well as comprehension and discourse are common areas of difficulty (Boucher, 2012). Impaired executive control of language functions contributes to communication problems in children with ASD (Loukusa and Moilanen, 2009). Executive functions are important for generating, selecting and organizing words into coherent sentences and paragraphs and sustaining meaningful conversations. Even when they have strong vocabulary and syntax skills, people with ASD have difficulty

fluently conversing and generating language on novel topics. There is greater reliance on scripted or repetitive language and on topics of special interest and familiarity to the speaker. Given (1) reduced neural response in key components of the fluency and EF networks and (2) selectively increased activity in areas of the LIFG associated with executive control processes, there appears to be a scenario whereby as search and retrieval demands increase, executive control centers for language in LIFG become functionally decoupled from posterior cortices associated with stored lexical information. Indeed, both on fluency tasks and in conversation, individuals with ASD struggle to generate words that are relevant to a context or topic, although it must be acknowledged that the link between real-world linguistic competence and fluency is not established.

1.5 Conclusion

Even when behavioral performance and verbal ability are equated, adolescent and young adult males with ASD show aberrant neural response during verbal fluency, a verbal EF task. Compared to NT males, they show reduced activation across frontal-striatal-cerebellar regions that have been associated with nonverbal EF in previous studies of NT and ASD individuals. This finding is in keeping with previous investigations of EF in ASD and extends them by documenting a similar pattern when a verbal, as opposed to visual problem solving, task is employed. The linkage found between RRBI and neural activation in some but not all of the predicted brain regions in ASD provides a preliminary indication that atypical neural activation may be associated with impairment in ASD. The ASD participants also show an atypical response within the LIFG to the letter fluency task specifically, with increased activity in a middle region of the LIFG that was found to be more active in ASD than NT controls in another investigation using a demanding word generation task (Knaus et al., 2008). When combined with evidence of reduced connectivity of the same area to the temporal lobe (Jones et al., 2010), our findings raise the possibility of a decoupling of EF and language brain regions in ASD that could be related to commonly observed difficulties generating original language during conversation.

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Highlights

This investigation extends previous work documenting reduced neural activation in autism during visual executive problem solving to a verbal task.

Reduced neural activity in autism was correlated with autism repetitive behavior symptoms in some but not all regions predicted.

Aberrant neural activity during fluency may relate to problems verbally able individuals with autism have with generating novel language in conversation.

Figure 1.
Average number of words produced during 10 second blocks for each fluency condition by group (ASD=Autism Spectrum Disorder; NT=Neurotypical). Error bars indicate standard error of the mean.

Figure 2. Differential neural activity during fluency tasks and automatic speech conditions

A. All Fluency Conditions versus the automatic speech condition (months). Regions in the blue spectrum were more active for the fluency tasks than for the months condition and regions in the yellow spectrum showed the opposite pattern. **B.** Letter versus Category fluency. Regions in the blue spectrum were more active for letter than for category fluency tasks. Regions in the yellow spectrum were more active for category than for letter fluency tasks. **C.** One versus two cues (Switch demand). Regions in the blue spectrum were more active for the two cues than the single cue condition.

Figure 3. Differential neural activity in ASD versus NT individuals during fluency tasks
Regions (in the blue spectrum) showing greater response in NT than ASD individuals. Regions circled in red indicate, **A.** anterior cingulate cortex, **B.** left anterior insula, **C.** left putamen, **D.** left premotor cortex, **E.** left insula cortex and fusiform gyrus, and **F.** the fusiform gyrus.

Figure 4. Group x Task interaction in LIFG

LIFG region defined by the Group X Task interaction (in the yellow spectrum). The interaction of Group (ASD, TD) X Task (Letter, Category) X Switch (one cue, two cues) was also significant in this region (shown in B). **B.** Histogram of percent signal change in neural activity during all of the category and letter fluency conditions for the ASD (red) and NT (blue) participants. Note: activity during automatic naming of months is shown for comparison purposes; this condition was not included in the analysis.

Table 1

Subject Demographics.

	ASD (n=17) Mean (st dev)	NT (n=20) Mean (st dev)	P value
Age (years)	16.03 (2.56)	17.05 (2.10)	0.19
Verbal IQ (standard score)	117.56 (13.58) ^a	111.70 (9.99)	0.15
Performance IQ (standard score)	111.81 (15.86) ^a	113.25 (9.20)	0.74
Handedness (right:left)	15:2	17:3	0.77
ADI social	20.88 (4.99)		
ADI verbal communication	15.29 (5.03)		
ADI restricted and repetitive behavior	6.53 (3.02)		
ADOS social	7.88 (3.22)		
ADOS communication	3.82 (1.74)		
ADOS stereotyped behavior	1.41 (1.73)		

^a
n = 16

Table 2Main effect of Group (ASD<NT, $q<.05$).

Location of Peak Activation	Talairach coordinates			Volume (mm ³)	t-value
	x	y	z		
<u>Frontal Cortex</u>					
LMFG Pre-motor	-21	-11	47	2466	4.897
L Cingulate	-8	22	37	1143	4.427
R Anterior Cingulate	10	22	29	814	4.132
L Anterior Insula	-28	14	6	1294	4.881
L Posterior Insula	-29	-34	19	980	5.021
LIFG Pre-motor	-53	3	15	325	4.320
LIFG Pre-motor	-42	0	26	202	3.724
<u>Temporal Cortex</u>					
L Fusiform Gyrus	-33	-38	-16	1652	4.795
L Fusiform Gyrus	-31	-54	-19	270	4.040
R Fusiform Gyrus	38	-62	-17	249	5.244
L Parahippocampal Gyrus	-20	-36	7	676	3.930
L Sup Temp Gyrus	-52	5	2	424	4.153
<u>Subcortical</u>					
R Thalamus	3	-16	11	1407	3.479
L Thalamus *	-8	-5	-2	505	3.918
L Putamen *	-17	5	4	614	3.479
<u>Cerebellum</u>					
L Culmen	-3	-68	-8	653	4.067
R Cerebellum	28	-43	-43	462	4.039
R Cerebellum	36	-50	-31	405	4.273
L Cerebellum	-21	-46	-32	399	3.979

* Brain activity in this region was correlated with ADOS restricted and repetitive behavior scores in the ASD group